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MODERN MEDICINE

ITS THEORY AND PRACTICE

IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS

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VOLUME IV

DISEASES OF THE CIRCULATORY SYSTEM—DISEASES OF THE BLOOD—DISEASES OF THE SPLEEN, THYMUS AND LYMPH-GLANDS

ILLUSTRATED

PHILADELPHIA AND NEW YORK

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PART I.

DISEASES OF THE CIRCULATORY SYSTEM.

CHAPTER I.

GENERAL CONSIDERATIONS IN CARDIOVASCULAR DISEASE.

By CHARLES F. HOOVER, M.D.

Introduction.—The problem for a physician to solve when confronted with a case of circulatory disease is, Which of the many factors in the maintenance of the circulation are at fault?

Briefly stated in a general way, he must determine if there is a faulty distribution of the blood, viz., in the peripheral vessels in the splanchnic area or in the pulmonary circulation; if the pure hydraulics of the circulation are maintained and if its accomplishment is fulfilled without an expenditure of more than a normal amount of work on the part of the heart. Some of these problems have their solution in phenomena purely physiological, some pathological, and some are still in the realm of theoretical speculation. Where physiology and pathology fail, the diagnostician can appeal only to recorded clinical symptomatology.

The factors in the normal maintenance of the circulation are: an efficient myocardium with a sound directing innervation, efficient and unobstructing valves at the atrioventricular and arterial orifices, an aorta and branches of suitable caliber with elastic walls. Furthermore, the aortic system must fade into small branches with walls of given elasticity and vasomotor tone. There must be an unhindered centripetal flow of blood in the veins, supported by the vasomotor tone of the venous walls, the valves, and contraction of the skeletal muscles.

We have not only the propelling agencies to consider, but also the aspirating forces in the thorax which assist the centripetal current of blood. These are the normal negative tension in the pleural cavity and the inspiratory effort in breathing. Another aspirating force is from the diastole of the heart, which we will see may have an importance equal to the systole, and in some instances of pericardial and myocardial disease a faulty diastole may be the chief cause of trouble. The problems thus far mentioned have

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to do largely with the systemic circulation and most circulatory disturbances, it is true, occur in this distribution, but the right ventricle and the pulmonary vessels may be the seat of trouble which is primarily in the pulmonary arteries or induced secondarily from diseases of the lung.

This discussion will be restricted to the consideration of a few of the physiological aspects of diseases of the circulation, and an attempt to show that this view of cardiovascular disease may engage the attention of a physician without the aid of any so-called instruments of precision.

Distribution of Blood.—If the equable distribution of blood in the body be disturbed, the cause must be in the central pumping organ or somewhere in the systemic or pulmonary vascular system. The most direct method of determining the site and character of the defect is to locate, if possible, a point where massing of the blood occurs. Massing of the blood at the proximal side of a lesion is often the source of symptoms which most attract the patient's attention, viz., cough and dyspnœa from pulmonary stasis, when the left side of the heart is primarily the seat of trouble or affected secondarily to some lesion of the aortic system; or discomfort in the hepatic region from stasis in the liver when the right heart is no longer able to propel a sufficient mass of blood. When propulsion of blood in the distal circulation is impaired, evidences of the character above mentioned are notably absent and the mass of blood accumulates in the splanchnic circulation, as seen in shock, depressor nerve influences, and vasomotor exhaustion in the terminal stages of infectious diseases. The same occurs in instances of reflex vasomotor dilatation in the abdominal vessels.

If there is impairment in mass movement of the blood, either of a positive or negative character, the first duty of the physician is to seek some evidences of an excessive accumulation which may be under increased pressure or under diminished resistance of the sustaining vascular walls. Dilatation of the splanchnic vessels is a common instance of the last-named condition. Stasis in the pulmonary circulation is by far the most common evidence of excessive accumulation of blood when there is any pure hydraulic distress in the cardiovascular system. Primary disease of the pulmonary arterial system is rare. Although the branches of the pulmonary artery have an abundant supply of muscular tissue in the structure of their walls, there is a very feeble vasomotor nerve supply. Such are the purposes of the pulmonary circulation that there is not the same demand for widely varying degrees of resistance in certain regions of supply, as in the aortic system. The respiratory function at any given time is the same in all parts of the lung; so there is no need of any device which will increase the supply to one portion of the lung over that of another part. What role vasomotor impulse plays in the pulmonary circulation is at present unsolved. Experimentally, no one has succeeded (by the usual physiological and pharmacological methods) in demonstrating a rise of pressure from vasoconstriction of more than about 20 per cent. of the normal pulmonary arterial pressure.

Some French physicians of note, however, have reported a goodly number of cases interpreted as vasomotor spasm of the pulmonary arteries caused by reflex stimuli from the abdominal viscera, chiefly the liver. It is a notable fact in the accounts of these that they improved under treatment which would be suitable for myocardial insufficiency from any source, viz., rest in bed, mercurials, and saline cathartics. Thus far the writer has never met with an instance which would bear such an interpretation. Experimentally,

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three-fourths of the pulmonary arterial branches can be tied off before there will be any evidences of insufficiency from the tricuspid valve or any diminution in the amount of blood delivered to the left auricle.[1]

Should the left ventricle fail to propel an amount of blood equal to that supplied from the right ventricle, there is directly an increase of pressure in the left auricle and pulmonary veins and finally in the pulmonary arteries. Von Basch[2] described this state of the pulmonary circulation as the rigid and distended lung. He conceived pulmonary stasis as an erectile state of the entire pulmonary vascular system which caused an increase in volume of the infundibula and impaired the elastic excursion of the lung, a state which could be legitimately described as a red emphysema in contradistinction to white emphysema, which is the atrophic form with a flaccid and anæmic lung. Von Basch used the following device to demonstrate his idea of the erectile state of an infundibulum in pulmonary stasis: A rubber tube, in a tortuous spiral course, through which a current of water was driven under pressure, was placed over the surface of an elastic, barrel-shaped bag of a certain resistance. As the tube elongated under tension of the fluid, the wall of the bag distended and aspirated water through its narrow opening. These conditions, however, are not analogous to those in the lung, where, instead of one such isolated infundibulum, there are myriads with their walls in direct contact. As a matter of fact, in the lung of vascular stasis, dilated and tortuous vessels encroach on the air spaces, and secondary changes in the capillary walls, infundibular walls, and bronchi are the factors of dyspnœa so far as the lung itself (independently of slowing of the blood stream) is concerned. Kraus[3] has shown, by direct observation on patients with severe cardiac lesions, that the respiratory insufficiency of pulmonary vascular stasis is not due to a mechanical defect in the lung. By analyses of the inspired and expired air of patients suffering from cardiac lesions the amount of air entering and leaving the lungs was shown to be the same as in healthy persons. There was not the same exchange of oxygen for carbonic acid as in normal conditions. Although there was an excessive ventilation of the lungs, there was a diminished ventilation of the blood due to the slowing of the blood current and the pathological changes in the lung above mentioned.

In cases of emphysema the same results were obtained. This suggests that the cause of the relief afforded to asthmatic patients by expiratory compression of the chest is due to acceleration of the blood stream by the pumping process and not merely increased ventilation of the lungs, as was formerly supposed.

In cases of pulmonary stasis we find the lower borders of the lungs occupying a lower position in the thorax than during the periods of fair compensation, but this increased volume of the lung is due to increase of volume which attends the emphysema of an accompanying bronchitis and increased effort at breathing. The increase in vascular volume of the lung takes place very largely at the expense of the infundibular air spaces. Although von Basch's conception of pulmonary stasis found many followers and the theory in itself was a very attractive one, it is not in accord with either pathological or physiological demonstrations. Obstruction to the pulmonary blood

[1] Conheim, *Lectures on General Pathology*, vol. i.
[2] *Physiologie und Pathologie des Kreislauf*, 1892.
[3] *Mass der Ermüdung der gesund und Kranken Menchen, Bibliotheka Medica*, 1897.

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stream either from increased resistance in the branches of the pulmonary arteries or from insufficiency of the left heart becomes apparent through diffuse bronchitis or pulmonary œdema and evidences of increased tension in the pulmonary artery. Œdema of the lungs is not an invariable accompaniment of a high degree of pulmonary stasis. In myocarditis accompanying acute infectious diseases, the writer has seen primary dilatation of the left ventricle, followed in thirty-six hours by great dilatation of the right ventricle. The tension in the pulmonary artery was so high that the pulmonary valves were not able to sustain the diastolic pressure in the pulmonary artery and a loud diastolic murmur appeared at the pulmonary orifice and was transmitted over the right ventricle. Myocarditis of the right conus arteriosus may be a factor also in causing the diastolic murmur. The murmur and evidences of high tension in the pulmonary artery disappeared promptly with recovery of the myocardium. During this period of cardiac failure there was not an adventitious sound audible over any point in the lungs. Stasis under high tension is not the sole requisite for œdema of the lungs.

A strong diastolic impact over the second intercostal space and third rib at the left border of the sternum is not sufficient proof of high tension in the pulmonary artery. This impact may be present on account of proximity of the right conus arteriosus to the anterior thoracic wall, which occurs when the left lung is retracted or the conus arteriosus dilated.

In addition to evidence gained by inspection, percussion, and auscultation, concerning the size and functions of the conus arteriosus, right ventricle, and auricle, other evidences of insufficiency of the right ventricle commonly present are signs in the bulbus venosus, external jugular veins, and in the liver. It is not uncommon to find a large pulsating liver in tricuspid insufficiency and no centrifugal, systolic wave in the external jugular vein. The presence or absence of the venous pulse will depend entirely in such cases on the closure or leakage of the valve in the vein above the bulbus venosus. The absence of swelling of the liver and hepatic pulse under similar conditions does not admit of such a simple explanation. There are no intervening valves in this instance; the swelling of the liver and its pulsation partly depend on the resistance of Glisson's capsule and the venous vasomotor resistance in the hepatic circulation.

Stasis in failing circulation is not always a matter of gravity and proximity of the lesion. Vasomotor influences also contribute, in many instances, to the site of massing of the blood. If massing of the blood in cardiovascular diseases were always an expression of hydraulic distress independently of physiological agents the problem would be much simpler than it frequently is. Regional stasis and regional œdema are occasionally encountered. A common experience in myocardial disease is to find an enlarged liver the sole sign of accumulation of blood on the proximal side of the left heart; at other times the signs may be purely renal and, in some instances, the signs may be wholly in the trunk or in the lower extremities. One instance particularly well illustrates this apparent inconsistency. The patient, a man aged forty years, had a septic endocarditis at the aortic orifice which terminated fatally in nine weeks. The lesion at the aortic orifice caused such marked stenosis of the orifice that it would just admit an ordinary lead-pencil. There was no insufficiency of the aortic valves. Clinically and pathologically the patient presented the appearances of pure aortic

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stenosis without insufficiency. During the illness the pulse rate was never above 50 and during the rigors, which occurred every few days, the pulse was as low as 36, when the temperature was 106°. It was a pure bradycardia. There were no signs of extrasystole or heart-block. The pulse was of course very small, monocrotic, and of the tardus type on the anacrotic side. The duration of the katacrotus was quite what one would expect from a pulse of such volume. There was nothing to suggest any great vasomotor changes in the aortic distribution. Dyspnœa was not severe; cyanosis was slight. There was little clinical or pathological evidence of stasis in the pulmonary circulation. The left ventricle was not at all dilated or hypertrophied and the right ventricle and auricle were very little dilated. The liver was enlarged, extending three inches below the costal border. There were more evidences of an accumulation of blood in the splanchnic distribution than in the lungs. The situation in this case corresponds very closely to Elie Cyon's[1] conception of the function of the cardiac depressor. The patient had a very feeble cardiac impulse, although the heart rate was slow and there were marked evidences of massing of blood in the abdominal organs and practically none in the pulmonary circulation. According to Cyon, irritation of the depressor nerve would account for bradycardia, weak impulse of the heart, and splanchnic hyperæmia.

Such an instance is a rare exception to the purely hydraulic sequence of events usually seen in valvular and myocardial disease, but instances very commonly occur in which signs of local massing of the blood occur when the ordinary signs of sequential hydraulic stasis on the proximal side of the lesion are not demonstrable.

In the early so-called erethistic stage of cardiovascular disease we commonly find the patient complaining of cough from pulmonary hyperæmia when we cannot demonstrate a high tension in the pulmonary artery secondary to passive dilatation from a dilated left ventricle. In other instances the liver may be the seat of discomfort and sensitive to pressure, when there is not a dilated right heart or a tricuspid insufficiency. Albuminuria from disturbance of the renal circulation may be present when the usual sequence of stasis from dilatation of the right heart is not demonstrable. All of these signs will sometimes disappear by employing some drug to lower the vasomotor resistance, such as nitrites or saline cathartics, and the improvement will not be accompanied by any perceptible change in the size of the right or left side of the heart.

Another example of distribution of the blood in cardiac disease not in accord with pure hydraulic sequence is pericarditis with effusion. We would expect stasis in the venous system on the proximal side of the right auricle, as in myocardial or valvular disease, but such is not the case. In pericarditis with effusion there cannot be hyperæmia of the lungs, as in cases of myocardial insufficiency, because pericardial pressure retards diastole of the right as well as the left heart. So far as the systemic circulation is concerned the distribution of blood should be the same as in a weakened and dilated heart from mitral disease, viz., low aortic pressure and dilated veins.

The veins are greatly distended in such a case, but unlike the picture of stasis from myocardial insufficiency, in place of livid and cyanotic lips the face and lips are strikingly pale. Given a case of pericarditis with effu-

[1] *Les nerfs du cœur*, Paris, 1905.

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sion and failing circulation, when the question of paracentesis arises, we can be safely guarded in our judgment by this single variation from the rule of blood distribution in failing circulation. If the patient's lips have grown pale with the progress of stasis, then withdrawal of the pericardial effusion is imperative. If his lips are livid and cyanotic we can be assured the obstruction is due purely to myocardial insufficiency and removing the pericardial fluid will not give relief. Just what vasomotor process is at work under these conditions is unknown, but the picture of stasis from pericardial tension strikingly differs from that in stasis from myocardial and valvular lesions.

The Heart's Impulse.—Under this heading we have to consider the excursion in systole and also in diastole. Modifications of the diastolic excursion may give very accurate diagnostic and prognostic information. There is no phase of cardiac diseases which is so variable and so inconstant in its significance as the cardiac excursion. A well-trained touch and sight are the only reliable means of observation in this field. The cardiogram, which may be used to graphically record what we see and feel is wholly unreliable when interpreted without control of sight and touch. The precordial impulse varies with the site of the cardiac region from which the tracing is taken. V. Frey[1] shows how widely the tracings vary when taken from different points on the exposed heart. The left ventricle near the lower portion of its left border, the right ventricle and right conus arteriosus (the sources of the precordial activity we ordinarily see and palpate in a patient) give very different tracings. So do the impressions gained by inspection and palpation over these areas vary in clinical practice. The negative and positive venous pulses and the carotid pulse are the only guides for determining the chronicity of phases of cardiac excursion. The accuracy with which these cardiac phenomena can be observed depends on the proximity of the heart to the anterior thoracic wall, which is determined by the size of the heart, the anteroposterior diameter of the thorax, and the volume of the lung.

When the heart is close to the anterior chest wall, as in adolescence, we can detect the downward and inward excursion of the apex during inspiration as clearly as portrayed by Röntgen rays. When the left and right ventricles are both dilated we can with relative accuracy define between the left and right ventricles and, in many instances of gallop rhythm, we can determine by palpation, as accurately as by auscultation, whether this comes from the right or left ventricle, and by comparing any phase of a precordial excursion with the pulses in the carotid artery and jugular vein we can determine whether an impulse is in the diastolic, presystolic, or systolic phase.

The old physiologists described the diastole as an active excursion of the heart's walls which forcibly opened the hand holding it within its grasp. Laennec described all impulses over the heart as systolic in time. To Bouilland (in 1835), however, the cardiac impulse was more than a mere systolic excursion. He recognized the share of diastole in cardiac impulses in chronic nephritis. We are indebted also to his countrymen for the best clinical analyses of the heart's impulse. Stefani,[2] a pupil of Luciani,

[1] *Die Untersuchung des Pulses*, Berlin, 1892, p. 109.
[2] Luciani, *Physiologie des Menschen*, 1905, vol. i.

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has given very convincing experimental proofs of an active diastole; so there is no longer any question about the mechanically active diastole. Whether or not this active diastole is due to contraction of muscles antagonistic to the systole is not yet proven. Stefani enclosed the heart of a dog in a cup which was closed at the base of the heart with the reflected pericardium. The cavity of this vessel was connected by a T-tube with a manometer and pressure bottle, and the pressure in the cava, carotid artery, and cardiac receptacle simultaneously recorded. He found that the heart was able to deliver a wave in the aorta when the pericardial pressure was 25 cm. H_2O higher than in the cava, *i. e.*, within the right ventricle. Furthermore, it was found, when the pressure in the aorta was reduced to a minimum by restraint to the diastole from pericardial pressure, if the peripheral end of the cut vagus was irritated, the pressure in the aorta rose. If the vagus was cut the aortic pressure sank. The deduction from this experiment was that if nerve irritation is able to increase the force of the diastole, muscular activity must be the agent to produce it. Whether we have a muscular diastole in an antagonistic sense or not is not clear, but this experiment teaches us that the diastolic precordial impulse is a physiological as well as clinical fact.

There are two points in the so-called long pause in which an impulse from the heart may occur, the diastolic phase in which the active diastole occurs and the presystolic period during which the auricle contracts. The former has the same chronicity as the diastolic murmur of mitral stenosis and the latter is synchronous with the presystolic murmur of mitral stenosis. Diastolic impulses of the heart have the same time relation to the systole as diastolic murmurs. The impulse may go over into the systolic impulse, thus giving the impression of a prolonged systolic impulse, or the diastolic impulse may be distinctly differentiated from the systolic impulse by a palpable and visible relaxation. The best examples of the latter are seen in cases of chronic interstitial nephritis and arterial sclerosis with high arterial pressure. This phenomenon is known as the double impulse. Very good examples of the less differentiated forms of diastolic-systolic impulse are seen in mitral stenosis and in myocarditis at the conclusion of acute infectious diseases, *e. g.*, influenza. The diastolic impulse of arteriosclerosis is a compensatory measure and a warning that the dilatation of stasis is impending and requires absolute rest and cardiac stimulation. Palpable and visible gallop rhythm in mitral stenosis is accompanied by other signs which are equally or more significant. In myocarditis, or toxic conditions, following infectious diseases, the palpable gallop (which is also audible) may be the only sign of myocardial impairment, but it indicates the necessity of rest until the heart muscle has fully recovered.

In synechia cordis there is a diastolic impulse which, however, has not the same active character as seen in the impending myocardial insufficiency of arterial sclerosis. The writer has seen only four instances of this phenomenon and in these the diastolic impulse alternated with a strong systolic retraction over the apex. Although the precordial forward excursion was sharply synchronous with a venous collapse, the precordial excursion was more like a slapping impact than the heaving excursion of the diastolic impulse of chronic nephritis. It seemed very plausible in these instances of synechia cordis that the diastolic impulse was a direct elastic rebound of the thoracic wall resulting from systolic retraction. The phenomenon persisted over so long a period in various stages of compensation and insufficiency

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that it does not seem possible that the diastolic impulse could have been due to active diastole of the ventricle.

Lenhartz[1] has suggested that the active diastole is responsible for hypertrophy of the left ventricle in cases of uncomplicated mitral stenosis. Only in diastole can there be any increased demand on the left ventricle in pure mitral stenosis, and there is sufficient clinical and laboratory evidence of the active diastole, as well as evidence of the diastole being directed by vagus function. Furthermore, there is good evidence of the diastole being associated with anabolic processes, and therefore a basis for hypertrophy of the left ventricle. When one considers the cardiac diastole as an active and essential function in maintaining the circulation, and the abundance of clinical and experimental evidences to support the view, we realize how essential it is to carefully look for some manifestation of it in our patients.

The diastolic share in a presystolic impulse may often be very misleading to an examiner. The presystolic impulse over the apex in myocardial affections may often be mistaken for a prolonged and systolic impulse when in reality it is the sum of a presystolic and systolic impulse which is palpated. This very often occurs in myocarditis and mitral stenosis in which presystolic impulses are common. The diastolic impulse which is common in aortic insufficiency and chronic nephritis can be easily recognized both by inspection and palpation. To the practised touch all these modifications of the impulse are more apparent than a cardiogram will reveal. The prolonged impulse, the presystolic-systolic impulse, and the diastolic-systolic impulse can be recognized by palpation alone. It is a misfortune for the physician to believe these refinements of diagnosis can be elicited only by the so-called instruments of precision. There is far greater danger of being misled by the apparatus than by the senses. By this statement the writer does not wish to minimize the scientific and clinical value of comparative tracings of the venous and arterial pulses and heart's impulse in studies of auricular and ventricular arhythmia, bradycardia, and tachycardia, but for the observations above mentioned all instruments of precision can be dispensed with.

Role of the Auricles.—We have seen there are two compensatory resources of the ventricles in maintaining the mass movement of the blood, viz., increased force of the systole and hyperdiastole. Do the auricles assist in these compensatory efforts? By the time a patient with chronic endocarditis (mitral stenosis, for instance) comes to autopsy we find a thin-walled and greatly dilated left auricle. At autopsy the observation usually stops with this information. To determine whether there may be an hypertrophy of the auricle requires the adoption of Miller's proposed method of separating all the chambers and weighing them apart from one another.

That the auricle does hypertrophy has been found clearly enough in patients with old mitral stenosis who have met with sudden death from other causes. The wall of the left auricle in such cases has been found as thick as the wall of the right ventricle. Such a demonstration of course requires the heart to come to anatomical examination while a fair state of compensation still persists. There are other pathological findings which indicate the dispensableness of the auricle. In veterinary literature there are a number of instances described in the horse in which the right auricle has undergone

[1] *Münch. med. Wochenschrift*, 1890, Nr. 22.

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complete calcification. The endocardium was intact, but the auricular wall was as hard and rigid as the shell of an ostrich egg. During life there were no signs of circulatory disturbances. There are, however, other instances of calcification of the myocardium of both ventricles where the mural structure at the atrioventricular sulcus was transformed into a rigid ring. The ventricular myocardium showed such extensive deposits of lime salts that section with a knife was very difficult and the papillary muscles were so involved that they projected into the ventricular cavity like rigid stalactites. From the descriptions, one is forced to believe the circulation was largely maintained by the auricles.

That the auricle is capable of throwing a wave of blood into the aorta is well demonstrated in the studies of pulsus bisferiens. D. Gerhardt found the first elevation of the carotid in a case of double pulsation of the artery to be synchronous with systole of the auricle. The writer has observed the same in a case of pulsus bisferiens. Hürthle has succeeded experimentally in demonstrating an auricular wave in the aorta. He did not produce a pulsus biferiens in his animal, but showed the auricle could develop a pressure equal to 20 mm. Hg. If, by irritation of the vagus, the aortic pressure was reduced to 12 mm. Hg there was then a slight elevation in the aorta which preceded the systole of the ventricle and was synchronous with the auricular systole. Such observations compel us to give some heed to the auricle as a motor organ.

It is a common experience, in combined stenosis and insufficiency of the mitral valve, to find only a presystolic murmur and thrill with a loud tympanitic systolic tone over the apex. There is no suggestion of mitral leakage, although insufficiency is as clearly present anatomically as the stenosis. When compensation is disturbed in such a case we have quite another picture. As signs of stasis develop in the pulmonary vessels, acute dilatation of the heart and arhythmia, the presystolic murmur and thrill disappear. We have instead a gallop rhythm over the apex of the left ventricle, and the systolic sound is either accompanied or obscured by a loud blowing murmur. The presystolic elevation and sound over the apex may be due to the hyperdiastole of the ventricle or to the wave from the dilated left auricle. As the dilatation of the heart and pulmonary stasis disappear we have restoration of the former conditions. Instead of the presystolic elevation and sound over the apex of the heart we again have a palpable presystolic thrill and a presystolic murmur; the systolic murmur disappears and we again have during the ventricular systole a loud, sharply defined, systolic sound. Samways attributes this series of events to the role of the auricle, and explains it in the following manner: The total pressure on the bounding walls of a hollow sphere increases directly as the square of the radii. The resistance of the walls of a hollow, elastic sphere, with a certain wall thickness, will be inversely as the square of the radius. Thus, the auricle in its contracted systolic phase has an obvious advantage over the dilated ventricle. Now, if we can conceive the systole of the auricle to be maintained longer than the usual time, the auricle would successfully guard the mitral orifice against regurgitation during the systole of the dilated ventricle. For, in the dilated state the contraction of the ventricle is much less complete than during compensation. Consequently, the ventricle remains at a physical disadvantage in its contention against the guard of the auricle. Such an explanation requires a great prolongation of the auricular systole. The systole of

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the auricle is estimated to occupy only one-third as much time as that of the ventricle; so if the auricle were to guard successfully the mitral orifice during the entire ventricular systole, it must prolong the time of systole four times that of the normal period. Such a conception is very inconsistent with the slight variation of systolic time of the ventricle under widely differing conditions.

Although this conception is repugnant to the purely physiological conception of the spacing of the cardiac cycle, it seems very possible that some such function on the part of the auricle must guard the so-called button-hole mitral orifice in the expulsion phase of the ventricular systole. Potain ascribes the presystolic elevation of the ventricle in gallop rhythm to the systole of the auricle, and possibly correctly, for it remains to be clearly shown whether this presystolic elevation is due to hyperdiastole on the part of the ventricle or to the passive distention of the relaxed ventricular wall by a wave of blood from the auricle. These considerations make it apparent that the auricle merits some serious consideration as a motor organ and may play a considerable compensatory role in the distribution of blood under pathological conditions.

Valvular Mechanism.—The wonderful elasticity and resourcefulness of the myocardium in adapting itself to varying demands from one moment to another has always elicited the admiration of students of physiology. Although not so obscure in their methods and structure, the perfect function of the valves guarding the atrioventricular and arterial orifices is not less marvellous.

The tricuspid and mitral valves are closed the instant the pressure within the auricle becomes less than the pressure in the ventricle, and that occurs independently of the ventricular systole. Experiment has shown that the flow of blood from the auricle into the ventricle forms eddies and currents between the wall of the ventricle and the cusps of the valves; so that there is a force at work in the current of the entering blood which tends to approximate the edges of the valves and is prevented from doing so by the pressure from the auricle. Directly the auricle ceases its contraction there is a force within the ventricle which (no longer hindered by the pressure from the auricle) seals the atrioventricular orifice. If this were not so, then there must of necessity always be a slight regurgitation attending every systole of the heart, and this we know is not true. The tricuspid and mitral valves are closed before the systole of the ventricles begins. In this manner the auricle shares in the production of the systolic sound. The ventricles now have a point of opposition for the expulsion of the blood into the aorta and pulmonary artery, respectively. There is an appreciable lapse of time between the commencement of systole and opening of the semilunar valves. This mechanism of the auricular wave closing the atrioventricular valves is probably responsible for the sound heard over the ventricle in cases of heart-block when the auricular contraction is not followed by a ventricular systole. There is a similar provision for the closure of the semilunar valves.

Ceradini[1] has used the following demonstration to show how the currents in the aorta contribute to the closure of the semilunar valves: A vertical glass tube is equipped with a piston at the bottom and the tube filled with water containing visible substances in suspension, so that the direction of

[1] Luciani, *loc. cit.*

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currents may be detected. The piston is pushed upward and with its upward progress the particles suspended in the column of fluid are seen to attain varying velocities. There is a central axial stream in which the speed is nearly double that of the average speed of the particles in suspension. The particles near the periphery of the tube cavity progress very slowly and are overtaken by the piston in its upward progress. These are swept into the axial stream by a centripetal current from the periphery; they are seen to fly before the piston in the axial stream and on reaching the top of the liquid are again carried toward the periphery by centrifugal currents. If the piston is stopped the column of fluid is seen to be divided into two parts. The central axial stream continues forward and the tardy peripheral stream reverts toward the piston. At the surface of the fluid a centrifugal eddy is seen, and at the piston a centripetal eddy, in which the visible particles are seen rushing from the periphery toward the central axial stream. This reverting eddy is believed to be the factor which closes the valves the instant the intraventricular pressure is less than that within the artery.

The attempts to mark with absolute accuracy on a cardiogram just when the closure and opening of these two sets of valves occur have not met with uniform results among various observers. One reason is probably the want of any perfect model of a cardiographic tracing. The tracing of the exterior of the heart is a combination of the contraction curve of the heart muscle and the ventricular volume. We have seen above, under consideration of the diastole, how widely this may vary and how the diastolic impulse may modify the excursion of the heart muscle; so also may the closure of the ventricular valves clinically occupy varying points on the precordial excursion. This will depend entirely on the character of the ventricular diastole, and how much of a precordial excursion is caused by the active diastole and how much of a precordial impulse is imparted to the ventricle from the systole of the auricle. So the presphygmic and "prosphygmic" rise of the precordial region are phenomena which will change with the demands and efficiency of the heart muscle. They are not constant factors under pathological conditions. It is an error to assume that the instant the palpable impulse of the heart begins the atrioventricular valves are closed and the semilunar valves are opened.

The active diastole of the ventricle, the passive distention of the ventricle by the current of blood from the auricle, and the closure of the atrioventricular valves before the beginning of the ventricular systole may all enter into the palpable precordial impulse. Failure to consider these factors will lead to misconceptions of the character of the systole of the heart. A so-called prolonged systolic impulse over the heart may be partly presystolic. By observing the waves in the jugular veins and comparing their chronicity with that of the carotid pulse and the duration of the precordial impulse, the examiner can arrive at just as accurate conclusions for diagnostic purposes as by the use of instruments for registration of these phenomena. So far as the practical diagnostic data are concerned in this relation, thoughtful inspection and palpation are the only means requisite for the diagnostician.

The time of closure of the semilunar valves is of course the instant the pressure within the ventricle is less than that in the aorta. The possible lapse of time between the closure of the aortic valves and the diastolic sound or impact is not appreciable and cannot be the source of any misconception of the cardiac cycle. The diastolic sound or the diastolic impact over the

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base of the heart or the aorta or pulmonary artery is taken as the point of closure of the semilunar valves.

Myogenic and Neurogenic Theories.—Investigation of myocardial diseases has, in recent years, given a new significance to the question of cardiac autonomy. How and where does the automatic stimulus of the heart originate? How do the nerves share in the cardiac activity? How is the coördination between the chambers accomplished? All these problems are resolved into the question: Is the autonomy of the heart myogenic or neurogenic in origin? Although the problem is unsolved there has been much of interest produced by champions of both sides of the question which has contributed to our knowledge of the myocardium and its nerve supply. These studies are the basis of modern views on cardiac arhythmia (Engleman and Wenckebach).

The myogenic theory has gained much favor among physiologists and clinicians:

1. There are pathological reasons for this view. Lesions of the heart muscle and skeletal muscles have little in common and lesions of the myocardium have a much closer analogy with diseases of glandular organs, viz., the kidney and liver. The myocardium is now regarded as a homogeneous blending of discrete structural cells. It consists of numberless branched chains of singly nucleated membraneless cells, between whose contractile substance the most intimate contact exists. There is supposed continuity of substance between the contents of several cells. This conception of the heart muscle is quite different from our idea of skeletal muscles.

2. Heart beat has never been produced by stimulation of any nerves supplying the heart.

3. Both vagi have been cut, and, after degeneration of the nerves had set in so that stimulation of the peripheral ends no longer affected the heart's rhythm or rate, the Stanius ligatures were applied, with the same results as when the vagi were intact.

4. The dog's heart has had all its nerve connections severed from the brain, spinal cord, and sympathetic system, and survived eleven months.

5. Transmission of contraction waves in the myocardium have been shown to be independent of the continuity of nerve structures in the heart muscle by making a series of zig-zag incisions through the wall of the turtle's heart parallel to the base. These incisions are made so that there must be a solution of continuity of all nerve paths from the base to the apex. Only muscular continuity is left, and that of course remains only through very narrow connections. In spite of these sections the rhythmic contraction wave is not abolished.

6. Development of electricity and heat shows the myocardium to be the seat of very active physiological oxidation. Recently new evidence has been added to show that cardiac autonomy is dependent on metabolic processes within the myocardium. Rhythmic contractions of auricles and ventricles have been restored in the human heart after postmortem removal of the heart from the body, by irrigating the myocardium through the coronary vessels with a nutrient artificial serum impregnated with oxygen.[1]

7. Embryological evidence shows that the rhythm of the heart beat is

[1] Kuliabko, *Pflüger's Arch. f. d. Gesamt. Phys.*, 1903, vol. xcvii; also Hering, *ibid.*, vol. xcix.

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established before cardiac ganglia (which are sympathetic in origin) have entered the heart. This evidence alone would be decisive if the negative could be absolutely proven, but the failure to demonstrate their presence does not prove their absence.

In spite of all this evidence contributing to the myogenic view, Kronecker[1] has shown that there is a centre in the dog's heart, located in the upper and anterior quarter of the interventricular septum, which, if pierced with a needle, will cause death. The trauma from such a procedure must be inflicted on a nerve centre, as otherwise so slight an injury to the heart wall could not cause death. Kronecker says the intracardiac ganglia produce the rhythmic contractions of the heart. "Even if the myocardium is capable of independent contractions under certain conditions, the muscle alone cannot do it. The myocardial ganglia receive and transmit stimuli from one chamber to another and thus maintain a rhythm and coördination between the several chambers which would be impossible if there were merely myocardial autonomy."

The neurogenic theory regards the ganglia of Remak at the junction of the vein with the auricle as the origin of automatic stimuli. These stimuli are transmitted along the network of nerves from auricle to ventricle. The halt between the systole of the auricle and the ventricle is conceived to be caused by the intervention of the ganglia of Biedert.

Recently, Uexküll[2] has presented biological evidences, from the study of simple forms of sea animals, which tend to harmonize the two views of automatic rhythm. He has shown the interdependence between muscle and nerve centre in automatic rhythm, the refractory period, and "all or nothing" law of contraction which is observed in the myocardium.

The champions of myogenic autonomy have given us an analysis of the basic factors of myocardial activity and have assigned their direction to the nerve supply. These factors are automatic production of stimuli, response to stimuli, transmission of stimuli within the heart, and contractility. According to Engleman[3] each factor can be modified in a positive and negative sense.

Those influences which affect the periodic contraction stimuli, *i. e.*, the heart rate, are known as chronotropic influences. Those controlling the contractile responsiveness of the myocardium to stimuli, *i. e.*, those which determine the minimum stimulus to which the heart will respond, are known as bathmotropic influences. Those affecting the transmission waves in the heart are known as dromotropic influences. Those modifying the strength, size, and duration of the contraction are known as inotropic influences.

A universal clinical application of these terms is not possible with our present knowledge of cardiac action. Engleman's analyses of heart action have proven of great service in facilitating propadeutics and dialectics on the subject, and the physician will find it valuable to think in these terms when analyzing the manner of a heart's action, particularly when bradycardia, tachycardia, and arhythmia come under consideration.

Arhythmia.—Investigations of cardiac autonomy have led to new conceptions of cardiac arhythmia. The basis of these studies is an analysis of pulsus bigeminus—which is regarded as an allorhythmia or pararhythmia

[1] *Zeitschrift f. Biol.*, 1897, vol. xxxiv.
[2] *Ergebnisse der Physiologie*, vol. iii, Abth. ii.
[3] *Pflüger's Archives* from 1895 to 1897

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due to extrasystole. Primary to the idea of extrasystole are several characteristics of myocardial response to stimuli which have been recognized for many years, viz., (*a*) "the all or nothing law of contraction;" (*b*) failure of the heart muscle to respond to stimuli during a certain part of the cardiac cycle known as the refractory period, and (*c*) the compensatory pause.

(*a*) Although vigor of response of skeletal muscle to nerve stimulus does not sustain a constant proportion to the vigor of the stimulus, still there is some constancy in the degree of contraction of skeletal muscles after varying magnitudes of stimulation. In the heart muscle this is not the case, no matter how strong the stimulus may be, if the heart responds at all it responds with all its strength. This is known as "the all or nothing law."

(*b*) During a ventricular systole the heart will not respond to any stimulus with an added contraction, however strong the stimulus may be. After the completion of the systole, irritability and contractility of the muscle gradually return until the normal period for the following systole occurs, when an automatic stimulus is released. The period in which the heart will not respond to any stimulus is known as the refractory period. In the succeeding period of available contractions, the earlier in the diastole a stimulus is applied the stronger it must be to elicit a response. As we approach the point in the diastolic phase for the following systole a lesser stimulus is required to produce a contraction. The occurrence of contractions in this period of relative refractoriness is known as the phenomenon of extrasystole.

(*c*) If the heart is now permitted to follow its automatic rhythm after the production of an extrasystole, it will be found that the pause following an extrasystole will be longer than in the normal automatic rhythm; if sufficiently long to make the distance between the first and third contractions the same, a systole of the normal rhythm could have occurred instead of the interpolated extrasystole. This lengthening of the diastolic time after an extrasystole is known as the compensatory pause. Extrasystoles are produced from irritation either of the auricle or the ventricle, which is the basis of many clinical examples of arhythmia.

Genuine arhythmia occurs, however, when there is a disturbance in the origin of automatic rhythm, viz., at the junction of the veins with the auricles. Genuine arhythmia is characterized by the absence of compensatory pause in the arterial pulse and the absence of signs of heart block in the jugular veins.

The pulse volume accompanying an extrasystole will be smaller than a normal pulse on account of the shortened diastole, rendering the filling of the ventricle incomplete. Many examples of arhythmia, bradycardia, and, indeed, some examples of tachycardia, can be explained on the basis of extrasystole. Although these phenomena above described have not furnished an explanation for all instances of cardiac arhythmia, they have furnished a very tangible basis for their experimental and clinical investigation.

Hypertrophy and Dilatation of the Heart.—The terms hypertrophy, accommodation, adaptivity, and compensation have been sources of a large controversial literature in medicine. As in most medical polemics, the kernel of controversy has been the use of terms rather than facts and clinical experience. One phase of the controversy has been the questioning whether a heart which has responded with hypertrophy to an increased demand on its work may enjoy the same amount of reserve energy as before.

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In other words, does the individual begin life with a certain number of foot pounds of energy on which he may survive a certain length of time, provided he draws on his reserve at a certain rate, or, should occasion demand it, may he increase his store of energy, meet an increased rate of demand, and still enjoy an available energy equal to his original endowment?

The heart is capable of performing very many times the sum of daily work which an ordinarily regulated life demands. This property it has in common with other organs. The lungs have a respiratory capacity five times that ordinarily employed. The same may be said of glandular organs, such as the kidney, liver, and glandular structures in the gastro-intestinal tract. We know the kidney and liver may enjoy a genuine hypertrophy and not sacrifice the working value of any of the total structure. Can we secure the same result in the heart, or does hypertrophy always mean an encroachment on the available sum of energy?

Under one condition at least hypertrophy is a welcome sign. At birth the right and left ventricles have the same wall thickness. With the beginning of extra-uterine life there is an increased demand on the left ventricle. To maintain the systemic circulation now requires a greatly increased expenditure of energy and the left ventricle responds to this demand with hypertrophy.

This physiological hypertrophy must also be accompanied or rather preceded by dilatation just as dilatation primarily accompanies the hypertrophic process from plethora or physical exercise. With the transition from intra-uterine to extra-uterine life, the enormous increase in metabolism in all the body structures will directly require a volume of the cardiac cycle greatly in excess of the prenatal demand. To meet this sudden demand the heart must dilate and subsequently undergo hypertrophy. This is a benign hypertrophy and as welcome as hypertrophied skeletal muscles to the athlete. By graduated exercises the athlete may increase the efficiency of his heart muscle as well as his skeletal muscles. In this connection it must be remembered that the athlete's myocardium is subjected only to periods of excessive work and merely the ordinary demands of life in many hours of waking and sleeping. The heart which is hypertrophied as a consequence of permanent changes in the cardiovascular system never has freedom from the increased labor. We sometimes meet with examples of pronounced impairment of the heart valves in a patient who has been wholly unaware of any discomfort which could be attributed to a defect in the circulation. These persons are capable of performing feats of strength and skill which would overtax many hearts we consider normal. There is no method of estimating the reserve energy in prospect for such an individual, nor is there any method of learning what his heart might have equalled without the valvular lesion. Sometimes we meet with great surprises in the exhibitions of reserve energy of a crippled heart.

Transition from a state of compensation to incompetence seems often very sudden. A patient is brought to the hospital with a greatly dilated and rapid heart, pulmonary œdema, hepatic stasis, and œdema of the legs. From the history we learn that this patient never experienced any symptoms which could have been due to an impaired circulation until a few hours before, when suddenly, while engaged in work, he experienced a sudden pain in the precordial region, attended with dyspnœa and great exhaustion. Insufficiency of the myocardium which develops suddenly is due to the

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vicious cycle created by lowering the pressure in the coronary arteries, which occurs directly the ventricle is unable to maintain the required aortic pressure. Thus, at the very time when the heart muscle requires the greatest supply of nutrition, the supply of blood to the myocardium lessens.

Fraentzel refers to a striking instance of the very sharp line which sometimes marks the transition from a state of comfort to one of painful incompetence. A patient suffering from myocardial insufficiency walked about the ward apparently in a state of comfort. On being asked why he did not go into the garden to walk, he replied: "If I go into the garden, I must climb several steps to return to the ward, and this effort costs me a night of shortness of breath without sleep."

Sometimes death occurs very suddenly without the slightest premonition of incompetence, as in cases of fatty degeneration of the muscular cells and myocarditis following acute infectious diseases, *e. g.*, diphtheria, scarlatina, variola, typhoid fever, and pneumonia. In other cases the myocarditis following infection may be indicated by very great dilatation of the heart, which recedes as the myocardium improves and the patient goes on to a good recovery. Why one case is attended with all the classical signs of myocardial insufficiency and terminates in recovery and the other ends in sudden death without the slightest dilatation as a warning remains a mystery. There is, too, great inconsistency between pathological findings and the clinical course of myocardial diseases. We must be content in our diagnosis of such cases to recognize the functional defects rather than the exact anatomical findings. If we can differentiate between myocardial disease as against valvular or arterial disease or disturbances of innervation, we will have kept within safe limits of diagnostic venture.

Many times the functional impairment will manifest itself long before anatomical changes occur and often great anatomical changes will occur before the slightest functional disturbance appears. Very extensive malignant disease of the heart muscle may be found without having given the least sign of functional disturbance as a part of the clinical course of the disease. Even in experimental myocardial disease there is not the loss of reserve energy we would expect. A dog is poisoned with phosphorus, which results in extensive fatty degeneration of the myocardium. If now the aorta be compressed, the heart will maintain a flow of blood against a pressure two or three times greater than the normal aortic pressure of the dog. The ability to maintain a pressure of 200 mm. Hg against resistance must not be interpreted, however, as being equal to maintaining 200 mm. Hg pressure as a result of physical exercise. The former instance is one of pure external resistance unattended with the great mass movement of blood in the aortic and pulmonary circulation and the greatly increased metabolic processes which occur in physical exercise. Thus, we see patients with arterial sclerosis maintaining an aortic pressure of 300 mm. Hg, or the pressure may change from 220 mm. Hg to nearly 300 mm. Hg without causing any discomfort. But the patient is not able to perform the slightest physical exercise without great discomfort.

A normal blood pressure does not imply normal blood movement. This is often a source of confusion to medical examiners. There is an apparent inconsistency between an arterial blood pressure nearly normal and pulmonary and hepatic stasis. This inconsistency is apparent, not real. Vas-

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cular contraction compensates for diminished filling of the vessel. Mitral stenosis offers very good examples of this condition.

Thus far we have had under discussion the compensatory or accommodative property of the heart in its systolic phase, but the diastolic phase probably plays as great a role. It is possible that some instances of death in myocardial disease are due to loss of its diastolic property. The diastole is not so easily studied as the systole, and at present our knowledge of the manner in which diastole is accomplished is so vague that the physiological knowledge of the subject cannot be applied to any known pathological changes in the myocardium.

We have seen how diastole enters into the compensatory measures of the heart in the beginning of extra-uterine life and in physical exercise. The same diastolic aid must be invoked in the compensatory procedures of aortic insufficiency, the plethora of gluttony, and in emotional excitation of the heart. If this dilatation gives the incentive to trophic changes in the myocardium, then an eccentric hypertrophy appears; the capacity of the chamber is increased and the ventricle can deliver a greater volume of blood under an increase of the total intraventricular pressure, with a smaller volumetric excursion of the cardiac wall. There may be changes in the circulation which demand an increase of the systolic effort without increased demands on the diastolic function, *e. g.*, increased vasomotor resistance. There follows then an hypertrophy of the wall without dilatation which is known as concentric hypertrophy. Later, when a concentric or eccentric hypertrophy of either ventricle is no longer able to maintain the resistance against which it is working, we have a passive dilatation with loss of tone of the heart muscle. This is known as the dilatation of stasis and is always accompanied by incompetency, while the active compensatory dilatation may be sufficient to increase sixfold the volume of blood (delivered by the systole of the ventricle) and compensation remains undisturbed.

In acute dilatation of the heart with stasis, which results from excessive exercise, there is lacking the trophic stimulus which, under favorable conditions, leads to hypertrophy. Whether or not this sequence of events occurs in a heart which is perfectly sound up to the time of dilatation is a question. It is possible that such hearts have experienced some lesion prior to the event which attended the dilatation. Such cases have been observed, but there are many other instances recorded in which the heart was functionally sound up to the time of the acute passive dilatation.

Dilatation and hypertrophy of the heart most commonly result from malformation or disease of the myocardium, the valves or pulmonary vessels, either primary or secondary to lung affections, or diseases of the aortic system. Purely psychical and nervous excitement may give rise to all the signs, viz., cardiac enlargement, arhythmia, and murmurs. The painful emotions especially, which are the more intense and lasting, bring in their train a series of objective and subjective symptoms which betray myocardial impairment. Grief or loss of fortune is sometimes the direct cause of these symptoms as well as prolonged anxiety and fear of death. Prolonged and uncontrollable laughter in a young healthy girl has been observed to be followed by acute dilatation and asystole. Excessive venery, gluttony in eating, and drinking of malt liquors are commonly recognized as direct causes of myocardial impairment. Frequent and prolonged efforts at coughing in acute and chronic diseases of the respiratory tract, when there

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is not sufficient involvement of the pulmonary vessels to be a contributing factor, is also an exciting cause for myocardial disease.

Toxic influence, as in nephritis and Basedow's disease, may cause both hypertrophy and dilatation of the heart. The writer saw one instance of clearly demonstrable hypertrophy and dilatation of the left ventricle with high arterial pressure in a woman who, for many years, drank regularly as much as ten cups of coffee a day. All these signs diminished in a few months after discontinuing the use of coffee.

In estimating the causative factors of any myocardial affection it is often just as important to learn the habits of life and social influences which surround a patient as to learn the history of preceding diseases.

The Work of the Heart.—Physiological experiment has shown the energy developed by the left ventricle to expel 60 cc. of blood against an intra-aortic pressure of 150 mm. of Hg is 122.4 gram-meters. The work necessary to give this volume of blood under such pressure a velocity of 0.5 meter a second is 0.72 gram-meter. It is apparent from this estimate that a very small part of the total energy expended is employed in giving the volume of blood its velocity. The great mass of work is represented by the pressure against which the ventricle is contracting. Such estimates, however, do not admit of direct incorporation into our estimates of the clinical valuation of work performed by a heart, nor do they give us any prognostic information. Diseases of the cardiovascular system mean much more than a mere problem in hydraulics; the problem of hydraulics is intimately and intricately linked with physiological problems, both vital and chemical, which take place in the muscles, glandular structures, lungs, central nervous system, and in the heart itself. We find the relation between the heart rate, blood pressure, and size of the heart maintains a very inconstant relation to the resources of the patient. We are often disappointed in clinical observations to find the patient derives little benefit from changes in the blood pressure which would seem to greatly improve the mass movement of the blood. Our limitations in clinical studies of the mass movement of the blood are the study of the blood pressure and duration of the pulse. The arterial pulse, which is an expression of the heart's work against peripheral resistance in a closed system of elastic tubes, is the only tangible phenomenon from which we can form an idea of the efficiency of blood hydraulics.

A very important factor, always to be investigated, is the elasticity of the aorta and its branches. The pulse in the smaller arteries is an expression of two pulses, the ventricular and the aortic pulses. That portion of the pulse which outlasts the ventricular systole is manifestly due to the elastic property of the aorta. The total energy must have its origin in the heart itself, but the aorta contributes much to the economy of that expended energy. The energy expended in stretching the aorta is stored up as potential energy, to be released as kinetic energy after the closure of the aortic valves.

The value of an elastic tube intervening between a source of liquid stream and its outflow at a terminal orifice of small caliber can be illustrated by the following experiment: An elastic outflow tube *A* is fitted to a pressure bottle. The tube *A* terminates in two branches, one a flexible rubber tube, the other a rigid glass tube. Both branches terminate in equal orifices, which have a caliber much smaller than the channels of the two branches.

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When the flow is continuous an equal amount of fluid escapes from the two orifices within a given time. If the stream be interrupted by rhythmic compressions at the rate of one a second, the volume of fluid which escapes from the flexible branch in a given time will be about double the amount which escapes from the rigid branch. The pressure of the head is the same in both instances; but the flexible branch gains much in time if the resistance of the orifice is sufficient to cause distention of the flexible tube. While the stream is released at *A* there will be a considerable amount of fluid stored within the elastic tube which will escape while the stream is interrupted at the trunk-tube *A*.

The elasticity of the aorta accomplishes the same result for peripheral circulation by maintaining a constant flow when the original source of pressure (the ventricle) is interrupted. Although the aorta does not contribute any energy for propelling the mass of blood, it does by virtue of its elasticity increase the pumping efficiency of the ventricle. Elasticity of the aorta affords advantage in time, in expenditure of energy analogous to the advantage of distance in the expenditure of power in a lever of the first class. If the elasticity of the aorta is lost, then we approach a condition in which the total mass movement of blood must be accomplished during the time of ventricular systole. Propulsion of blood toward the periphery during ventricular diastole is largely sacrificed. Therefore, the same mass movement of blood in a much shorter time will require a greater maximum pressure than under normal conditions when the elastic aorta contributes during cardiac diastole the potential energy stored during a cardiac systole.

From these considerations it is quite clear how the hydraulics of the circulation in chronic aortitis are identical with those of insufficiency of the aortic valves, viz., a great and sudden excursion of the artery during systole and a katacrotus of short duration, a capillary pulse and loud pistol-shot tone in the femoral artery, and hypertrophy of the left ventricle. If resistance to the peripheral flow be diminished by depressor motor influences, then there will be a pulse of short duration, a capillary pulse, and loud pistol-shot tone in the femoral artery. In one case of this character the pistol-shot tone in the femoral artery was so loud that it was distinctly audible at a distance of six feet from the patient; this sign disappeared after the administration of adrenalin.

Flow of blood in the artery may have the same character in widely differing conditions, viz., insufficiency of the aortic valves, aortitis, and depressor motor influences. Differentiation between these causes must be arrived at by study of other factors besides the arterial flow.

Duration of the pulse beyond the closure of the aortic valve is an expression of aortic elasticity contending against peripheral resistance and internal friction or the viscosity of the blood. The character of the katacrotus can be modified by the volume of the systolic wave from the ventricle, the elasticity of the aorta, the viscosity of the blood, and the vasomotor resistance.

Dicrotism is an expression of differentiation between the ventricular wave and the wave from aortic contraction. To accentuate dicrotism above the normal degree, the favorable conditions are diminished peripheral resistance and a shortened systole of the ventricle. The indispensable factors for dicrotism are an elastic aorta and a certain relaxed vasomotor tone. There must be sufficient vasomotor tone to compel distention of the aorta

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during the ventricular systole, and there must be sufficient elasticity of the aorta to store a considerable amount of blood during the heart's systole. Vasomotor paralysis causes the dicrotic wave to disappear. This is seen in the progress of meningitis, typhoid fever, and sepsis. Particularly in typhoid fever and sepsis is the transition from dicrotism to pulsus celer a marked feature with the progress toward vasomotor exhaustion. The need of elasticity of the aorta for an expression of dicrotism was well illustrated in two patients with typhoid fever. One was a young man with a sound aorta; the other a man aged sixty-five years with aortitis which was manifested by dulness to the right of the sternum in the second intercostal space and a palpable diastolic impact in this situation. Although both patients had a heart rate and blood pressure nearly the same, the pulse of the young man was markedly dicrotic and the old man had a monocrotic pulse of the celer type.

Shortening of the cardiac systole will bring out dicrotism as seen in two conditions which differ very widely in other respects: the hyperdicrotism after prolonged muscular effort as described by Kraus, and the hyperdicrotism of paroxysmal tachycardia as exhibited in the case of a tabetic patient described by Pal. In hyperdicrotism after physical exercise we have another factor which contributes to the manifestation of dicrotism, namely, arterial relaxation. It would be impossible to have dicrotism with a high arterial maximum pressure without arterial relaxation. In the latter the tonometer registered a maximum pressure of only 60 mm. Hg, whereas in the athlete the maximum pressure is increased directly after exercise. In both cases, however, there is sufficient shortening of the expulsive phase of ventricular systole to cause the ventricular and the aortic wave to alternately reach the distant arteries.

If the vasomotor resistance is greatly increased, then dicrotism is obscured by the heightened aortic and arterial tension and the oscillations of elasticity which give the picture of pulsus durans and prolonged katacrotus.

A prolonged katacrotus and high maximum pressure are not invariable accompaniments. Occasionally one meets with a greatly prolonged katacrotus in the brachial artery where the artery literally struggles to empty itself during the cardiac diastole, although the tonometer reveals a normal maximum pressure. In such cases we are not dealing with a widely spread increased peripheral resistance, for if the carotids and femoral arteries are examined we may find the katacrotus much shortened. The controlling factor, however, is resistance in the splanchnic distribution, and the pulse in this area is not accessible. It is thus clear how important is an examination of all the accessible arteries, and how misleading the pulse in a single artery may be.

The character of anacrotus and katacrotus are far more important than the maximum blood pressure in estimating the hydraulics of blood flow. There is no instrument of precision which suffices for this purpose. The sphygmogram, like the cardiogram, is only of service when controlled by trained observations of sight and touch. For purposes of graphic comparison it is useful, but it cannot be substituted for trained observation. Various modifications of the tonometer have proven to be of much greater service than the sphygmograph. Although the general use of the tonometer may be attended with a considerable margin of error, it nevertheless has enabled observers to communicate and record their observations with

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relative accuracy. Before the employment of this instrument there were no means of approximately recording and comparing our observations on blood pressure. The purposes for which the sphygmograph were designed were anticipated even by Galen, who graphically portrayed pulse sensations, and very clearly, too, so that the reader can recognize most of the characteristics of pulse tracings which have a physiological significance to the modern clinician.

With blood pressure, however, the matter is very different. We are dealing with a single attribute which cannot be described in terms other than a standard of measurement. The trained touch can accurately recognize an increase or diminution of pressure in one of the larger arteries, such as the brachial, carotid, or femoral, but the tactile experience of an examiner is not communicable to others, nor can it be stored in the examiner's memory for comparative studies.

The tonometer, like other instruments of precision, has served to stimulate physicians to better tactile observations on the pulse. Peripheral resistance can be estimated only as expressed in the peripheral flow and the modifications of the anacrotus and katacrotus of the pulse.

In addition to the elasticity of the aorta and its branches and peripheral resistance from the capillaries and minute arteries the only factor of resistance to the arterial flow of blood is in its viscosity or internal friction.

Of all these factors the only one which can be estimated clinically with accuracy is the aortic resistance. As above mentioned, the bulk of the work of the left ventricle is expended on stretching the aorta and its branches. This element of the work can be measured with the tonometer. All the other factors which modify the flow of blood can be estimated only by the senses.

Dyspnœa.—Dyspnœa from disease of the cardiovascular system may be pulmonary, toxic, or nervous in origin. The causes of pulmonary dyspnœa are the slowing of the blood current in the lung, thus impairing the interchange of oxygen and carbon dioxide. Besides slowing of the blood current there is a secondary bronchitis consequent upon stasis and the disease in the alveolar epithelia and thickening of the blood capillary walls. All of these conditions contribute to the production of chronic dyspnœa. Toxic sources of dyspnœa in disease of the circulation are not chemically proven; we have nothing more than the direct association between increased renal elimination and the relief of dyspnœa. It is not an uncommon experience, in observing cases of arterial sclerosis, to see a marked disproportion between the degree of dyspnœa and the relative size of the left and right heart, pulmonary stasis, and massing of the blood. There may be no œdema, slight evidence of massing of the blood either in the pulmonary circulation or in the liver, and no albumin in the urine, and yet, after the administration of diuretics, such as caffeine, and theobromine preparations, we find from the brisk diuresis there has been a decided retention of fluid within the body and apparently with some toxin, for directly diuresis is accomplished the dyspnœa is relieved. The disproportion between the physical evidences of retention in such a case and the dyspnœa is seen in other cases of valvular lesions: pronounced œdema in pendent parts, very considerable massing of blood in the liver, and very much less difficulty in breathing. The kidney is not the only organ which may be associated with the production of toxic dyspnœa, for with disturbance in venous and capillary pressure come changes in osmotic pressure and metabolism of the organs,

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so that the liver may be the source of an intoxication in two ways: one by the failure to protect the organism against toxins already formed and possibly by the production of toxins of its own. So far as clinical experience goes in these cases, we are justified in speaking only of the renal source of dyspnœa. With this, however, we do not mean there is always a lesion of the renal structure; nor is it perfectly clear that the work of the kidneys independently of structural disease is responsible for the condition. We are not justified in going farther than to state that common clinical experience teaches that when there is a disproportion between the physical manifestation of disturbed blood distribution and dyspnœa, we find the patients gain great relief by stimulating the kidney to increased activity.

The purely nervous source of dyspnœa is not so clear as either of the forms above described, yet there seems sufficient clinical evidence, moderately well supported by experiment, to show the reasonableness of this source of dyspnœa in cardiovascular disease. The nerve supply of the heart and lungs is not only anatomically closely linked, but there is a very close clinical relation between the two. It is sometimes very difficult to differentiate between dyspnœa consequent upon subacute or chronic circulatory disturbance in the lung and dyspnœa due to a pure nervous reflex which is quite independent in its circulatory disturbance from the basic disease. The nervous relation between the heart and digestive tracts is more apparent in clinical experience. It is common to see vomiting, meteorism, and great subjective distress, referred to the stomach and even the bowel, associated with myocardial disease, particularly the acute disturbances which result from diseases of the coronary arteries. We know there is a trophic influence on the lung embodied in the functions of the vagus nerve, as evidenced by pulmonary œdema and acute emphysema due to disease of the nerve trunk and the vagus nuclei. Acute bronchial asthma with emphysema (both spasmodic in character) occur in diseases of the mediastinum, and acute pulmonary œdema is an occasional incident in the history of diseases involving the bulbar nuclei. There are two classes of reflex dyspnœa in cardiovascular disease. One is from the stomach and the other from the aorta and left ventricle. The act of digestion requires an increased supply of oxgyen and an increased mass movement of the blood, and, in this way, may suffice to induce dyspnœa in a patient with an uncompensated cardiac lesion. In many patients with cardiovascular disease, particularly with those having diseases of the coronary arteries, dyspnœa is precipitated directly after taking very moderate amounts of food, and that, too, when there are no signs of stasis in the pulmonary or systemic circulation. It seems this dyspnœa must be the result of a diffuse reflex vagus stimulus to the heart and lung, for it is manifestly disproportionate to the reserve energy the heart exhibits in meeting demands of muscular exercise. One patient with syphilitic aortitis described his suffering in the following manner: "I am able to walk about with comparative comfort, but I am starving from want of food; I am hungry, but afraid to eat. Directly I take the smallest amount of food I cannot breathe, and have intense pain over my heart and down the inner side of my arm. If I eat nothing I am comparatively comfortable and able to attend to my business."

Diseases of the aorta are particularly liable to be accompanied by paroxysmal attacks of dyspnœa. These patients are commonly awakened in the early hours of the night, sometimes with precordial pain and other times

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with mere feeling of anxiety and distress in breathing. On examining such patients we are surprised to find very slight evidences of any change in the circulation from those we have been accustomed to see in the patient from day to day. Although the patient is extremely dyspnœic at ten o'clock at night, the same day he was comparatively comfortable so far as his cardiovascular disease was concerned. We are surprised and disappointed, in making a physical examination, to find the blood pressure and volume of the artery little changed; and, although we regard the dyspnœa as cardiac in origin, there are not the usual evidences of stasis in the pulmonary circulation. The patient has loud breathing, prolonged inspiration, and expiration; there is even an absence of the coarse, moist rales we find in the ordinary bronchial asthma.

François-Franck has shown by animal experiment two effects upon the lung from stimulation of the inner coat of the aorta at the valvular orifice and just above the valve. The first effect was on the pulmonary arterial branches and the second on the bronchi. There is a reflex spasm produced in both. The spasm of the bronchi is assumed because there was an increase in the resistance to distention of the lung and an increased resistance to insufflation of air in the bronchial tract (this experiment was done on the curarized animal). François-Franck observed also in these experiments cough and spasmodic closure of the glottis. The blood as a result of these experiments contained a diminished amount of oxygen and excess of carbon dioxide. There is a very striking consistency between the clinical picture of these cases of reflex paroxysmal dyspnœa and the animal experiment. Spasm of the bronchi and contraction of the pulmonary arteries would produce a dyspnœa with cyanosis without rales. Some cases of cardiac dyspnœa may be explained by François-Franck's theory, although it must be admitted that this explanation has not as clear an experimental basis as we would wish for such a common clinical experience.

Cardiovascular disease is attended with another form of respiratory distress, which is also quite independent of the gross hydraulics of blood distribution. It is very probable that many such instances are explained in many quarters by the intricate and ingenious theory offered by François-Franck, when, in reality, they are explainable on a much simpler basis. A man, aged sixty years, has occasionally awakened in the night (for the past three years) with intense air hunger which compelled him to sit upright in bed and breathe very deeply for a period of about five minutes. He did not have dyspnœa in an etymological sense. He suffered from air hunger and hyperapnœa. During his waking hours he never had any respiratory distress. For three months his wife observed that these attacks were always preceded by complete cessation of respiration. The patient had alternating periods of apnœa and hyperapnœa, the so-called Biot's type, which is a modification of the Cheyne-Stokes type of respiration, and is produced by the same factors which cause the latter. It was then observed that apnœa developed the moment he would go to sleep, and after about a minute of apnœa the patient awakened with intense air hunger and hyperapnœa. The wife then discovered that the period of air hunger and hyperapnœa did not occur if her husband was closely watched and awakened the instant the apnœa was apparent. For three months it was her practice to watch her husband as he went to sleep, and if apnœa ensued she awakened him instantly, for if spontaneous awakening was awaited the air hunger

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and hyperapnœa caused intense distress. As a usual thing the patient would have to fall asleep from five to twelve times before sleep could be procured without the supervention of apnœa. This patient had marked arterial sclerosis of the Gull and Sutton type, with the usual cardiac and renal signs. His systolic arterial pressure was 200 mm. Hg. The carotid pulse had a prolonged katacrotus, so that it was fair to assume there was extensive sclerosis in the brain arterial supply. There was a small margin of accommodation in the total bed of the brain arterial supply. Immediately on falling asleep there was sufficient anæmia of the respiratory centre to render it hypo-æsthetic, and apnœa persisted until the accumulated partial pressure of carbonic acid in the blood was sufficient to arouse the hypo-æsthetic respiratory centre; whereupon, the patient suffered from air hunger until the partial pressure of carbonic acid in the blood was again reduced to its normal point. After repeated attempts at going to sleep the patient was able to procure sleep, which, however, was not so profound as he would have had if the apnœa had not interrupted it. His later sleep was not attended with the same reduction in the blood supply to his brain as attended the deep slumber in the early part of the night. The slumber apnœa ceased promptly after the administration of nitroglycerin and citrate of caffeine.

Another patient with a similar experience had the Stokes-Adams syndrome and heart-block, with an arterial pulse rate of 30 and a jugular venous pulse rate of 120. For nearly five months it was necessary to watch this patient every night and arouse him every time he fell asleep, because apnœa developed immediately he went to sleep. It was not until the early morning hours that he could procure sleep without apnœa, and this sleep he said was very light. This patient had a syphilitic infection seven years before and showed marked sclerosis in all his accessible arteries. There were in this instance two possible sources of the slumber apnœa, viz., heart-block and sclerosis of the basilar arteries. Under prolonged and vigorous treatment with mercurials he recovered simultaneously from heart-block and slumber apnœa.

In medical literature we find frequent comments on nocturnal dyspnœa which awakens patients out of a sound sleep, but is unaccompanied by any signs in the lung or circulation to account for the respiratory distress. A notable feature of all these cases is arterial sclerosis with chronic aortitis; Huchard and François-Franck have seized upon this point as the source of a reflex vasomotor effect, as above described. In such cases we are really dealing with a bulbar symptom. If patients are closely watched we find slumber apnœa precedes the air hunger and hyperapnœa on awakening. Another fact in support of this view is the character of heart disease in which the Cheyne-Stokes and Biot types of respiration are produced after the injection of morphine. All these patients have arterial sclerosis and no doubt the bulbar arteries share in the process. There is a moderate depression of the respiratory centre not sufficient to cause apnœa, but if the added factor of morphine be supplied there is sufficient hypo-æsthesia of the respiratory centre to produce either the Cheyne-Stokes or Biot respiration.

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CHAPTER II.

DISEASES OF THE PERICARDIUM.

By A. McPHEDRAN, M.B.

ANATOMY OF THE PERICARDIUM.

The pericardium is the serofibrous sac enveloping the heart and the first portion of the great vessels. The outer fibrous layer forms an irregular cone or pyramid with its base resting on, and intimately attached to, the central tendon and adjacent muscular substance of the diaphragm; its truncated apex surrounds the root of the aorta and pulmonary artery and is continued on them for about two inches as a tubular prolongation, becoming gradually merged into their external coats. Anteriorly it forms the posterior boundary of a small triangular area behind the lower part of the sternum, the anterior mediastinum; the remainder of its anterior and all its lateral surfaces are in contact with the pleuræ. Posteriorly it forms the anterior boundary of the posterior mediastinum, being in contact with the aorta, œsophagus, trachea, and root of the left lung. The phrenic nerves lie one on either side, as they pass down to the diaphragm.

The inner or serous portion of the sac consists of two layers, a visceral and a parietal. The parietal layer lines the outer fibrous coat of the pericardium from which it is reflected on to the great vessels, surrounding about an inch or an inch and one-half of their origin and enclosing them in acommon sheath, and is thence continued downward over the heart which it envelops and to which it is closely adherent as the visceral layer of the pericardium, —the epicardium. The pericardium retains the heart in position, and, by the serous fluid which it secretes, it facilitates the movements of the heart. The arteries of the pericardium are small; they are derived from the superior phrenic, the anterior mediastinal, and the bronchial. The veins accompany those arteries and are branches of the brachiocephalic. The lymphatic vessels enter the lymphatic glands which surround the superior vena cava.

PERICARDITIS.

We usually apply the term pericarditis to inflammation of the serous layer of the pericardium. This is not quite correct, inasmuch as the inflammation may, and often does, extend through the external fibrous layer and affect the surrounding structures; and also inward into the muscular structure of the heart itself, and, at its thinner portions, possibly through to the endocardium. Pericarditis occurs so very rarely by itself that it cannot practically be regarded as a distinct disease (Sibson).

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History.—The occurrence of exudation into the pericardium was known to ancient authors; mention is made of it in the works of Morgagni, Rondelet, and others. It was not until 1749, when Senac described it in his work on the heart, that reference was made to it as a clinical condition. Auenbrügger, by means of percussion, demonstrated the occurrence of dulness in pericardial effusion and thus gave the clinical nature of the malady a certain definiteness. But it was only after the discovery of auscultation by Laennec, that in 1824, Collin, his chief clinical assistant, demonstrated the pericardial friction sound and interpreted its significance. It is said that Laennec himself had heard the friction sound but failed to appreciate its meaning and importance; he speaks of it as like the creaking of leather. Then followed the contributions of many observers, such as Louis, Andral, Stokes, Skoda, and later Sibson, making the knowledge of the condition and its relationship to other diseases very full. Little further advance could be made until the discovery of the bacterial causes of disease. Since then the bacteriology of pericarditis has been very fully elucidated by the works of Talamon, Netter, Baute, Weichselbaum, Babinsky, and many others.

Etiology.—Pericarditis is usually described as either *acute* or *chronic*. This is a convenient division, but it is clinical rather than etiological.

The correctness of the classical division into *primary idiopathic pericarditis*, and *secondary pericarditis*, is becoming more and more questioned as the infectious nature of the malady is more generally conceded. *Primary* or *idiopathic pericarditis* has usually been attributed to chill or trauma, the two chief causes that have always been cited in support of the theory of idiopathic inflammation. Now, the theory seems untenable since bacteriological researches have taught us the real pathogenical influence of chill and trauma. It is reasonable to believe that chill and trauma cause pericarditis in the same manner as they cause pleurisy, pneumonia, or peritonitis, that is, by disturbing the circulation and thus lowering the nutrition and vital powers of the pericardium below the point necessary to enable it to successfully resist the invasion of pathogenic bacteria whose virulence may, from the same cause, be increased.

Pericarditis probably results from a general, rather than a local, chill. In susceptible persons the chilling causes congestion of the pericardium, and the lowered vitality resulting may enable the bacteria carried to it by the blood to excite inflammation. Most of the cases of primary pericarditis are probably due to rheumatism, of which a microbic cause is becoming more and more widely conceded. However, any pathogenic organism may be the exciting agent. Probably not a few of the cases of obscure origin are tuberculous. Osler believes that plastic pericarditis is frequently tuberculous, although the tubercles may easily escape detection, being covered by the fibrinous exudate.

Similar observations apply to *traumatism* as a cause. The injury may come from without or within. In penetrating wounds it is no longer necessary to argue that the inflammation is due to microbic invasion; inflammation will not follow an aseptic wound.

A contusion of the chest may rupture small vessels in the pericardium, and the areas of extravasation will offer little resistance to microbic invasion, as will also abraded areas of the pericardial surface. Pericarditis has been caused experimentally in small animals by injuring the pericardium by blows, or by the application of ice to the chest wall, after injecting staphy-

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lococci into the general circulation.[1] Of micröorganisms, the pneumococcus is probably the most frequent cause of pericarditis; the paricardium alone may be the seat of infection.

Trauma from within may arise from a foreign body, as a needle or a bone lodging in the œsophagus and passing through into the pericardium.

Secondary pericarditis is probably more frequent than is usually admitted. There are few, if any, infectious diseases that may not implicate the pericardium, either by bacterial invasion or by irritation of toxic substances.

Two modes of infection have been described: first, *extension by contiguity*, the inflammation extending from a neighboring organ or tissue; and, secondly, by *involvement of the pericardium in a general infection.*

Direct extension of inflammation is probably very rare. In pleuropneumonia in which it is said to occur, the invasion of the pericardium is not by extension of the inflammation from the pleura, but by infection of the pericardium by pneumococci brought from the lung, generally by the blood, but sometimes by the lymphatic circulation. Some believe that the pericardium is more often infected at the same time, and from the same source, as the lung, and not secondarily to it.

Even in pericarditis accompanying lesions in the mediastinum, of the large vessels, the bronchial glands, the œsophagus, the thoracic wall, and the diaphragm and abdomen, the inflammation is probably always due to the conveyance of microörganisms to the pericardium by the blood or lymph circulation, or at least only exceptionally by extension from contiguity.

In empyema, and thoracic or subdiaphragmatic abscess, the pericardium may be involved by rupture into it of the purulent collection, but even in these, infection probably precedes the rupture.

Of the diseases with which pericarditis is associated, *rheumatism* is much the most frequent. This was first pointed out by Pitcairn in 1788. From the ages of five or eight to twenty-five years, the rheumatic infection is especially prone to attack the heart, and cause pericarditis and endocarditis, and varying degrees of myocarditis especially when the pericardium is affected. As age advances, the heart is less and less frequently affected, and, on the contrary, the joints are usually more severely attacked. On account of the great influence of age on the liability to infection of the heart and its membranes, the general statistics of pericarditis without reference to age are very variable, and, therefore, of little value. In young persons, even with mild attacks, the heart rarely escapes; it is often the only part affected. Next to malignant endocarditis, pericarditis is the most serious form of heart disease in rheumatism (Poynton).

Williams believes that the pericardium is affected in 75 of every 100 cases of acute rheumatism, while Latham in 136 cases of rheumatism met with pericarditis in only 7. Ball and Sibson give 20 in every 100; Wunderlich, 19 in 100, and many others give about the same percentages. Sturges, in 100 fatal cases of heart disease occurring at Great Ormond Street Children's Hospital between June, 1881, and April, 1882, 54 being of rheumatic and 46 of non-rheumatic origin, found that in only 6 were there no signs of pericarditis.

The recent bacteriological investigations of Treboulet, Wassermann, and Paine and Poynton afford apparently conclusive evidence of the infective

[1] Rubino, *Arch. ital de biol.*, T. xvii; cited by Petit, *Traité de Med.*

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nature of rheumatism, a minute diplococcus being the active agent. These microörganisms have been isolated from the pericardial and joint fluids, and tissues of patients suffering from acute rheumatic fever, and, after culture on suitable media, their inoculation into rabbits has produced the usual lesions of acute rheumatism.

In common with the endocardial lesion, pericarditis is usually described as a *complication* of rheumatism. It is, however, just as essentially a primary lesion as the joint affection, and in the young it is often the only local lesion in the attack. In older persons it is most liable to occur in the severe cases with polyarthritis, especially if joint after joint is affected. This has been attributed to the excessive action of the heart in such cases, the overstrained structures being more susceptible, or less resistant, to the virus. However, the joint involvement may be slight; in not a few, pericarditis is associated with tonsillitis only. Many of the idiopathic cases are of this kind. The pericarditis usually becomes evident in the second week of the rheumatic attack. Hughes met with it from the sixth to the tenth days; Sibson before the eleventh day in more than half his cases; and Bamberger up to the fourteenth day. Thus the occurrence of pericarditis, at the height of the disease, favors the view that it is not a metastasis, but bears the same relation to the rheumatic affection as does the arthritis.

Sibson, however, met with pericarditis between the twenty-fifth to the sixty-third day in 7 out of 63 cases. He found that its occurrence is not nearly so dependent on previous rheumatic attacks as is endocarditis. There appears to be increased liability to pericarditis in cases of chronic endocarditis in which the heart is dilated and hypertrophied. In some cases the pericardial affection precedes by several days the articular manifestations. Such cases are reported by Graves, Stokes, Trousseau, West, and others. Males are much oftener affected with rheumatic pericarditis than females, but the greater liability of the male occurs probably only after maturity, and may be accounted for by exposure and overstrain.

Chorea is quite frequently associated with pericarditis, or more frequently still with endopericarditis. The cardiac affection may precede the choreic movements. There was pericarditis in 19 of 73 autopsies in cases of chorea collected by Osler; in only 8 of these was there a history of arthritis.

Pleurisy and *pneumonia* are, after rheumatism, probably the most frequent pathological conditions associated with pericarditis.

Pleurisy co-exists with pericarditis very often, both affections being due to the same general infection, such as that of acute rheumatism. The pericarditis has usually been considered as occurring by direct extension of the inflammation from the pleura, but it is more probably caused by primary infection of the pericardium in all cases.

Pneumonia is complicated by the secondary development of pericarditis usually in proportion to the severity and extent of the disease in the lungs. The danger of infection is least when an upper lobe is affected, and is much less when the disease is unilateral than when bilateral. Preble[1] says the liability to pericarditis in unilateral pneumonia is in the ratio of 1 in 40 cases; in bilobar and trilobar 1 in 10; and in quadrilobar 1 in 5.

In the experience of most writers, pericarditis occurs more frequently in association with affections of the right lung than of the left. In 31 cases in

[1] *American Medicine*, June 15, 1901, p. 482.

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Osler's service at the Johns Hopkins Hospital the right lung was affected in 13 cases, and the left in 5; both were diseased in 13 cases. Pneumococci were found in the pericardial exudate in 19 cases; in the remainder the exudate was sterile. There was pleurisy in 28 of the 29 fatal cases, the right side alone being affected in 13 cases, the left in 8, and both in 7.[1] The experience of other observers coincides fairly well with these results. Of the microörganisms, the pneumococcus is the one most frequently found in pericardial exudates.

Gonorrhœal infection is not a rare cause of pericarditis. First pointed out by Fournier, it was later admitted by Ricord and Raynaud. The gonococcus of Neisser has been found in the exudates of the pericardium as well as of the joints. Pericarditis may be associated with endocarditis due to the same cause. It occurs at very variable intervals after the infection of the genital tract, even as late as four or five weeks.

Tuberculosis of the pleura or the lung frequently precedes that of the pericardium. Tuberculous pericarditis may be a part of general tuberculosis, but more usually it develops subsequently to infection of the mediastinal glands, of the lungs, and of the pleuræ. Cases have been met with in which the pericardium was the only part affected. Scaglios[2] reports an instance in a woman in whom the pericarditis was the sole lesion. He says only 7 similar cases have been published.

In *typhoid fever* pericarditis is a rare complication. In McCrae's series of 1500 cases it occurred only in 3.

Chronic nephritis is acknowledged by all observers to be a cause of pericarditis, but there is much difference of opinion as to the frequency with which the association of the two diseases occurs. Sibson,[3] after very patient investigation, places the average at 8.1 per cent.; this is probably a fair estimate. He found pericarditis rare in acute scarlatinal nephritis of young persons. It occurs most frequently in chronic diffuse nephritis and in contracted kidney. It is not rare in lardaceous disease. As to the exact pathogenesis of pericarditis in nephritis there is much uncertainty. In cases in which the nephritis is due to an infection, the pericarditis may be excited by the same infectious agent as causes the renal lesion. In other cases, during the course of chronic nephritis, the pericarditis may be caused by some general infection, as rheumatism, pneumonia, or scarlet fever, or be a secondary infection, as in pyæmia, for which the nephritis and the cardiac changes have prepared the way by lowering the vital resistance of the pericardium. In both these groups the pericarditis may be serofibrinous or purulent, and is caused by pathogenic microörganisms, of which the pneumococcus is the most common.

In many cases, however, the exudate is found to be sterile, which is regarded as sufficient ground for the view that the toxins retained in the body on account of the defective function of the kidney in nephritis, are sufficient to excite the pericardial inflammation, just as the toxins of pathogenic microorganisms are capable of causing inflammation in this and other serous membranes. While it may be admitted that toxic substances may be effi-

[1] Chatard, *Johns Hopkins Hospital Bulletin*, October, 1905.
[2] *Deut. med. Wchnschr.*, 1904, xxx, 873; *American Journal of the Medical Sciences*, January, 1905, p. 157.
[3] Reynolds' *System of Medicine*, vol. iv.

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cient causes of pericarditis, it is nevertheless probable that the great majority of these cases are due to bacterial infection of one kind or another. The pericarditis is fatal in the great majority of such cases, and it may therefore occur as one of the forms of "terminal infection," which is usually the cause of death in chronic diseases.

Special Pathology.—The lesions of pericarditis may be limited to a part, more or less extensive, of the serous membrane—*circumscribed pericarditis;* more frequently it involves the entire pericardium—*diffused* or *generalized pericarditis.*

Circumscribed pericarditis is usually confined to the upper part of the pericardial sac, especially the cul-de-sac about the base of the aorta and pulmonary artery. It is generally limited to the anterior part, affecting first and chiefly the visceral layer, and later, to a less extent, the corresponding parietal layer. Quite frequently it is found on the whole anterior surface of the heart and on the corresponding parietal layer, being the parts that are exposed to the impact of the heart during systole.

The inflammatory process shows itself as an injection of the capillary network at the bases of the great vessels and along the course of the coronary vessels in the interventricular grooves. There is desquamation of the endothelium, so that the surface loses its glistening appearance, and becomes dull with many red striæ due to dilated vessels. These changes occur on both the visceral and parietal layers. The infection often extends to the contiguous tissues.

Inflammation of the pericardium presents the same anatomical variations as are found in the other inflamed serous membranes, the pleura in particular. There may be only congestion and fibrinous exudate, *pericarditis sicca;* or, in addition, abundant liquid exudate into the cavity—*pericarditis with effusion.* In both cases the exudate may be absorbed and the pericardium restored to its normal condition; more frequently, however, the inflammation leads to the formation of granulation tissue beneath the exudate, and this is organized, causing thickening of the pericardium, with or without adhesion of the opposing surfaces.

These inflammatory processes are due to infection by pathogenic microorganisms brought to the pericardium by the blood or lymphatic circulation, or to an accumulation in the blood of toxins of bacterial or tissue origin; the constant result is irritation of the serous membrane and the production of the various forms of pericarditis. It is possible, but not probable, that inflammation of adjoining tissues may extend to the pericardium by simple contiguity of tissue, but even in these cases, at least with rare exceptions, the pericardium is infected through the lymphatics.

Acute Pericarditis.—1. *Congestion and Fibrinous Exudate.*—The first manifestation of inflammation of the pericardium consists in a hyperæmia from dilatation and injection of the capillary vessels; the membrane presents a rose or red color, more or less intense, with a visible vascular network, and often minute ecchymoses, especially in young children. These changes are most marked in the visceral layer, but occur also in the parietal layer of the pericardium. In the lightest degree of inflammation there occurs some increase of the ordinary pericardial fluid, which usually also becomes somewhat opalescent from emigrated leukocytes and desquamated epithelium. The exudate seldom terminates with only these alterations, as the pericardium is highly disposed to the formation of a high grade

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of fibrinous exudate. This occurs in the lighter cases as an oozing, which forms small granules on the surface of the pericardium, giving it an opaque appearance; the presence of the exudate is readily demonstrated by gently scraping the surface with the blade of a knife. The fibrin masses are partly granular, partly hyaline, and under them lies the epithelium, chiefly non-nucleated and flat. These changes occur chiefly on the visceral layer of the pericardium, and may rapidly extend over the whole surface of the heart. The parietal layer in contact with the affected parts of the visceral layer soon becomes infected and undergoes similar changes.

If the inflammation is more severe, a greater amount of fibrinous exudate is formed. The pericardium becomes soft, thick, and, owing to the proliferation and destructive desquamation of its epithelial covering, assumes an opaque, velvety appearance. This phase is of very short duration, being soon followed by a fibrinous exudate, which is at first easily detached from the serous surface, but soon becomes more adherent. It is semitransparent, gelatinous, and yellowish in color. As new layers are formed, the exudate presents a stratified appearance and becomes thick and opaque; it may show, here and there, red areas from extravasated blood.

Owing to the movements of the heart, the surfaces of the exudate on the two pericardial surfaces in contact take on an irregular, papillated, or honey-combed appearance. Ridges may be formed, those on the surface of the heart having their counterparts on the parietal surface of the pericardium which is in contact with it. The surface has been compared to a variety of appearances: two patties of butter compressed together and then suddenly torn apart (Laennec); tripe, or the second stomach of ruminants; honey-comb; the tongue of a cat, etc. It may, however, show a markedly villous appearance, hence the appellation *cor villosum* or *hirsutum*. If there is much fluid present the fibrinous exudate may accumulate in large processes and present a mammillated appearance. Occasionally these processes extend and become attached to the opposite pericardial surface, and, later, become organized into fibrous bands.

In most of the acutely infective cases, masses of microörganisms are formed in the fibrinous exudate, which may invade the myocardium.

2. *Liquid Exudate.*—In the great majority of cases of diffuse pericarditis, particularly in those due to rheumatism, there is a *serofibrinous* exudate. Usually it is not of great quantity—from 3 or 4 to 12 ounces (100 to 350 cc.); rarely more than a pint (600 cc.); but over 60 ounces (1800 cc.) have been found present. In a boy, aged twelve years, with acute tuberculous pericarditis, the writer removed by aspiration on one occasion 38 ounces (1140 cc.), and a few days later, 45 ounces (1350 cc.) of blood-stained serum.

The exudate is usually clear, transparent, and straw-colored, but may be greenish; it may present small flakes of fibrin in suspension, or be more or less opaque from the presence of leukocytes, *seropurulent;* or of red blood corpuscles, *serosanguinolent;* or in more extreme cases it may be *purulent* or *hemorrhagic*. In the clear exudate, leukocytes, endothelial cells, and shreds of lymph are present in varying quantity; the opacity of the fluid will increase in proportion to the abundance of these elements.

Red blood corpuscles are frequently present in the exudate of tuberculous cases. Blood-stained serum has also been met with in *Bacillus coli communis* infection.[1] An excessive proportion of blood is rarely found except in

[1] Stewart, *Edinburgh Medical Journal*, 1904, vol. xv. p. 158.

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purpura or scurvy, in which the quantity of effused blood may be very great, exceeding the quantity of effusion in any other form of pericarditis. Ryan reports having found as much as ten liters of fluid, chiefly blood, in scorbutic pericarditis. Hemorrhagic exudate occurs also in cancer, Bright's disease, alcoholism, and cachectic states. It is characterized by the presence in the liquid of a marked proportion of red corpuscles, or the deep stain of an abundance of blood pigment. The false membrane is also deeply colored. Some degree of hemorrhage is not rare in acute pericarditis of the aged, especially in arteriosclerosis. The hemorrhagic exudate of the eruptive fevers is to be regarded as the result of an extreme toxæmia.

Purulent exudates are usually such from the commencement of the attack. They are more or less fluid and opaque, depending on their richness in leukocytes. The internal surface of the pericardium in purulent cases presents an ulcerated appearance, resembling a suppurating surface. The sac is in reality an abscess cavity, and the pus may penetrate the wall and burrow in any direction. It may discharge through an intercostal space or even above the clavicle, and form a pericardial fistula with or without pyopneumopericardium resulting.

Early in the inflammatory process in pericarditis the connective tissue becomes the seat of leukocyte infiltration, the lymphatic vessels become distended with exudate, and the bloodvessels with blood. By the third or fourth day, on the surface of the pericardium, appear numerous proliferations of capillary loops which penetrate the deeper layer of the plastic exudate and furnish it with a blood supply. At the same time also, in the deeper parts of the exudate, numerous polymorphonuclear leukocytes and large embryonic cells appear which in time are converted into new connective tissue. In the early period of this process the plastic exudate forms a grayish semi-transparent layer with the new vessels appearing as red lines buried in its substance. With the development of the new connective tissue the plastic exudate is completely absorbed. If the inflammation is slight, the new tissue formation is scant and confined to a few small, white, thickened areas on the surface of the heart—maculæ tendineæ, or "milk spots." In some cases there are only a few spots, while in others they are numerous and occur on all parts of the surface of the heart and great vessels. Frequently thread or band-like processes are found connecting the visceral and parietal pericardial surfaces. Processes may be found attached to some of the macular spots and hanging loose in the pericardial cavity; these are found most frequently at the apex of the heart and are probably produced by rupture of bands which had united the two surfaces of the pericardium.

If the pericarditis is marked so that there is abundant fibrinous exudate, and the inflammatory processes persistent so that there is much new tissue formation, the two layers of the pericardium may become completely adherent obliterating the cavity—*adherent pericarditis*. In most cases the fluid and plastic exudate is absorbed, but some remnants may be left and become caseous or the seat of cretaceous deposit. In rare cases the new-formed fibrous adhesions of the pericardial surfaces become infiltrated with lime salts, forming large calcareous plates which may coalesce and enclose the heart in a hard, unyielding *calcareous tunic*.

In mild cases the inflammatory process is confined to the pericardium; in severer cases the pleura and mediastinal tissues may be involved and result in pleural adhesions and extensive indurative mediastinitis.

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In certain infectious processes the exudate from the beginning is sero-purulent. This is most likely to occur in pyæmic cases, as well as in those of pericarditis secondary to purulent inflammation in the mediastinum, the pleura, and the mediastinal glands; also to ulcerative processes of the œsophagus, the stomach, etc., rupturing into the pericardium. The rupture of an air-containing cavity into the pericardium will give rise to *pneumo-pericardium.*

The bacteriological examination of purulent pericarditis shows a great variety of pathogenic microörganisms, of which streptococci, staphylococci, and pneumococci are the chief; the pneumobacillus of Friedländer, and the *Bacillus coli communis* are also met with, and Babinsky reports having found the *Bacillus pyocyaneus* in children.

3. *Period of Absorption or Organization of the Exudate.*—After a longer or shorter duration in cases not terminating fatally, absorption usually sets in. In those with serofibrinous exudate, even when abundant, absorption of the serum may take place in a few days leaving only the fibrinous part. The absorption is doubtless effected by the perivascular lymphatics, their permeability being restored. The fibrinous exudate in some cases fortunately undergoes granulation and is absorbed; the epithelium is reformed and all traces of the affection are removed. But this is the exception; more frequently the false membrane is long in being absorbed; beneath it is formed granulation tissue in which new vessels are developed, ending in the formation of new connective tissue and causing thickening of the pericardium. The opposing surfaces of the pericardium may become adherent over greater or lesser areas, and even universal obliteration of the pericardial cavity may take place.

Organization of the granulation tissue may take place without adhesion, and form plaques of greater or less extent of fibrous thickenings covered with endothelium. These are found at autopsy as whitish, opaque areas; they are especially frequent in the aged, and are designated by various authors as "milk spots." These smooth, white, opaque, pearl-like spots may be roundish or oval, sometimes irregular or band-like. They occupy chiefly the anterior surface of the right ventricle and the neighboring coronary groove, sometimes the point of the heart. They consist partly of lamellæ of connective tissue and partly of elastic tissue, and seem to be formed by proliferation of the pericardial connective tissue. By the majority of observers they are regarded as inflammatory in origin (Paget, Rokitansky, Strümpell, and Cornil and Ranvier); while others look upon them as simple nutritive processes and often due to senile changes.

Lesions in the Neighboring Tissues.—As already pointed out, inflammation of the fibrous tissue outside the pericardium often occurs, *a fibropericarditis.* In many cases of acute pericarditis the inflammation extends to the adjacent pleura, and the connective tissue surrounding the aorta and great vessels. It may be secondary to pleurisy or aortitis, or occur independently, and be excited by the same pathogenic cause. These lesions may lead to the formation of adhesions and fibrous bands, more or less closely uniting the pericardium to the sternocostal surface and to the great vessels; they may give rise to the symptoms met with in *adherent pericardium.*

In the lungs there may be atelectasis from compression by the distended pericardium.

The *cardiac* changes are of the utmost importance. The co-existence of

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endocarditis is frequent; it may precede or follow the pericarditis, the infection extending from one to the other serous surface, by the lymphatic vessels especially probably through the thin wall of the auricle, or through the walls of the large vessels; or both affections may arise at the same time and from the same pathogenic cause. *Myocarditis* is, in some degree, probably present in all cases of pericarditis, and chiefly to it are due the symptoms of dyspnœa and circulatory disturbance in pericarditis, especially in the absence of large effusion. If the infection of the myocardium is extensive, there will be granular and fatty degeneration of the muscle fibers. The wall of the heart will be flaccid, friable, pale, and in many cases, ecchymotic. These changes are most marked in the superficial layers of muscular fibers, those immediately subjacent to the pericardium. Owing to the loss of tone in the muscular tissue, the cavities of the heart dilate.

These myocardial changes, if extensive, cause grave symptoms, and are often rapidly fatal. In illustration may be cited the case of a boy, aged five years, who had had a short illness of an uncertain nature. When first seen he was sitting up in bed, with anxious facies, labored breathing, and a rapid, weak pulse. The area of precordial dulness was moderately increased, the heart sounds were weak, and the rhythm disturbed; there were no signs of disease elsewhere. He grew rapidly worse and in three days the illness terminated fatally. At autopsy a great fibrinous deposit was found on the pericardium, the specimen being a typical example of the *cor villosum*, and there were extremely marked acute degenerative changes in the myocardium.

In the chronic cases the areas with degenerative changes become gradually replaced by fibrous tissue.

Symptoms.—Owing to the multiplicity of forms, and the numerous modifications of the course of the disease in the same form of pericarditis, the symptoms present great variety. Further, they are often so masked by the associated diseases that pericarditis frequently runs its course without being recognized; in fact, it is not rarely the case that its existence even when sought for cannot be satisfactorily determined.

As a rule, there are general symptoms of constitutional disturbance, such as rise of temperature, frequent pulse, disturbed action of the heart, some dyspnœa with increased frequency of breathing, and a varying degree of precordial pain and distress. In children, disturbance of sleep may be the only complaint; there may be night-terrors and some delirium on waking. There is, in all cases, some enlargement of the heart from dilatation; it may be demonstrable in the earliest stage. But the only distinctive sign of pericarditis at its onset is the presence of a *to-and-fro friction sound*, occurring with the movements of the heart, and caused by the rubbing together of the roughened pericardial surfaces.

In view not only of the latent course in many cases of pericarditis, and the absence of definite symptoms in many others, but also of the frequency of the complete masking of the most characteristic phenomena by the associated diseases, it is of the utmost importance that the possibility of the implication of the pericardium should be constantly borne in mind in every case of rheumatism, pneumonia, nephritis, and heart affection, in order, if possible, to discover the disease at its onset. Daily examinations of the heart should be made in all these affections, the liability to pericarditis not being forgotten. This is of especial importance, if, in any of the above-mentioned affections, there is sudden elevation of temperature, delirium, or

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any marked disturbance of the nervous system, especially in children, for which a definite cause is not apparent. Even with the utmost precaution, more than a probable diagnosis is impossible in many cases, especially with pneumonia.

In primary pericarditis, and in other forms in which the affection is severe, subjective symptoms generally attract attention. *Pain* is usually present; Sibson found it in 70 per cent. of his cases. In most cases it is diffuse in the thorax, with precordial oppression; it may be increased by movements, deep inspiration, and cough, and by external pressure. It appears to be due to the inflammation of the serous membrane, and, according to Babinsky, is always severe in children. It may be referred to the shoulder or the left scapular region. But it is oftener referred to the epigastrium, where, in some cases, it is very severe. In these cases the diaphragm is fixed and immobile. Occasionally there is immobility of the diaphragm even when there is little pain. The late Dr. Barlow[1] directed attention to this as a valuable diagnostic sign, and reported the well-known case of the boy who tightly belted himself because he was relieved by preventing movement of the lower part of the chest and abdomen. Owing to contact of the pericardium with the œsophagus, the taking of food and drink may be painful.

In many cases, besides diffuse tenderness in the precordial portions of the intercostal spaces, special tender points may be found in the course of the phrenic nerve, the first point being above the clavicle between the two chief insertions of the sternomastoid muscle, and the second in the epigastrium between the costoxiphoid cartilage and the costal margin. Other points may be found in the intercostal spaces along the left margin of the sternum.

In certain cases pain, as described by Stokes, occurs in paroxysms like true *angina pectoris*. The pain begins in the precordium, extends to the left side, and is accompanied by numbness in the left arm, dyspnœa, palpitation, irregular action of the heart, anguish, tendency to syncope, and coldness of the extremities. The attacks have been attributed to extension of the inflammation to the cardiac plexuses and the phrenic nerve. They are of grave significance, not rarely terminating suddenly in death.

Attacks of paroxysmal pain of this character occurred in a young man in the Toronto General Hospital. He had a sharp attack of acute rheumatism with polyarthritis, which was growing less severe when the pericarditis, whose existence had been suspected owing to the disturbed action of the heart, frankly declared itself. The myocardium became greatly involved and great dilatation of the heart followed. There was apparently also much pericardial effusion, as not only did the area of precordial flatness extend much beyond that of apparent cardiac impulse, but there was dulness and very marked tubular breathing over an area about two inches wide below the angle of the left scapula.

Dyspnœa is a very frequent symptom. Sibson found it marked in 49 of 63 cases. It may be due to three or four local causes acting separately or in various combinations—pain, pericardial effusion, pleural effusion, and pulmonary collapse. To these should be added marked dilatation of the heart. In these latter, the dyspnœa is apt to be paroxysmal as in the case above referred to.

[1] *Medical Times and Gazette*, September 5, 1857.

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"With pain over the heart and pericardium, the breathing is hurried and distressed, while it is slackened and relieved with the relief of suffering; with the increase, the acme, and the decline of pericardial effusion, we have an increase, an acme, and a decline in the number of respirations; a second wave of increase in the amount of pericardial effusion leads to a second wave of increase in the number of respirations; and the respirations are also again accelerated, if, in the later progress of the case, pleurisy should spring up from the spreading of the pericardial inflammation; or if pulmonary apoplexy should declare itself, especially if combined, as it usually is, with notable pleurisy."[1]

The *pulse*, in the early stage, is usually rapid, but otherwise unaltered. Later, as the blood pressure falls much it becomes irregular and may be dicrotic. These alterations are probably caused by the associated myocarditis. In some cases with large effusion there may be a manifest *pulsus paradoxus*.

The *temperature*, in most cases, is moderately elevated, especially in young persons; it may remain elevated for some time, but with some irregularity. In chronic nephritis, and in cases with old-standing cardiac lesions, it may be only slightly elevated, but more often normal or even subnormal.

Sleep is usually disturbed by the pain and restlessness; it may be prevented altogether. *Cough* is not uncommon. It is short and dry, similar to that frequently occurring in pleurisy, and may be caused by pressure on the trachea. An anxious and distressed expression is frequent, even in the absence of pain. It is probably indicative rather of myocarditis than of pericarditis. Occasionally there is vomiting and hiccough. The voice may be altered, even lost, probably from pressure on the left recurrent laryngeal nerve.

Physical Signs.—In the first stage, inspection and percussion give negative results unless the diaphragm is immobile on account of the irritation of the pericardium. Later, with effusion (4 ounces or more), there may be some abnormal prominence of the precordial area if the chest wall is resilient; this is, therefore, rarely seen except in children and in young adults. In persons of more advanced age the appearance of prominence is due chiefly to fulness of the intercostal spaces arising from paresis of the intercostal muscles caused by prolonged pressure or extension to them of the inflammation. The pressure of the effusion may depress the diaphragm, only, however, in case of large effusions, as room is made for the smaller effusions by collapse of portions of the lung.

Pericardial friction is the sign of greatest value in that it indicates the rubbing against each other of the two roughened pericardial surfaces. It was first heard by Laennec, who likened it to the creaking of a saddle; but it was not properly interpreted until described by his assistant, Collin, in 1824. The friction sound or vibration occurs in both the systolic and diastolic movements of the heart, hence designated as being a to-and-fro sound or vibration. The friction is not quite synchronous with the cardiac movements, and is generally easily differentiated from the heart sounds. It is usually heard first at the base of the heart, less often along its left border over the lower end of the sternum, or at the apex of the heart; later it may

[1] Sibson, Reynolds' *System*, American edition, vol. ii, p. 508.

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become general over the whole surface of the heart, but more often extends gradually toward the apex, in the meantime disappearing at the base.

The character of the sound varies greatly; it may be soft like rubbing of tissue paper, or harsh like the creaking of new leather or like the noise of scraping or scratching of rough paper, especially in chronic cases. It is superficial, and may even seem to pass between the thoracic wall and the ear of the observer. It is increased by firm pressure with the stethoscope; Gibson points out that, if the pressure is too heavy, it may be weakened or even arrested, especially if the heart is weak. It is weakened and may even disappear as the pressure is lessened. It is usually increased when the erect position is assumed and lessened in the recumbent posture. Exciting the heart's action may also increase it.

It is almost pathognomonic, as the pericardial change necessary to produce it is almost always a dry pericarditis. In some cases non-inflammatory dryness or loss of smoothness of the serous surface, ecchymoses into the serous membrane, and "milk spots," may cause a pericardial friction sound, especially if cardiac hypertrophy increases the energy of the heart's contraction, as was shown by Stokes and Graves.

The *respiratory movements* have a variable influence on the area and intensity of the friction sound of pericarditis; in some cases it is loudest in expiration, in others in inspiration. Its area is often increased below during inspiration and less often above in expiration (Sibson). An important characteristic is the slight degree in which it is propagated; it is almost always limited to the precordial area, and often to a small part of that, corresponding to the portion of the pericardium over which it is produced. There are some exceptions to this, however, especially during the decline of the effusion; Sibson, in one case, found the friction sound audible over the greater part of the front of the chest, especially downward. The position, extent, and limited area over which the pericardial friction sound is heard is characteristic and in marked contrast to the wide diffusion of endocardial murmurs.

The *fremitus* or *vibration* of friction, if marked, may be felt by the hand placed on the precordial area. It is felt as a peculiar vibrating or scratching sensation, usually when the sound is loud and rough, and gives the impression of being quite superficial. It lacks the vibratory character of the thrill of mitral stenosis.

The duration of the friction sound is very variable, in some cases lasting but a few hours, and in others throughout the greater part of the course of the disease. Its disappearance may be due to (1) absorption of the exudate on the pericardial surfaces; (2) adhesion of the opposing surfaces, or (3) increase of the exudate, plastic or serous. If the heart be held against the wall of the chest by adhesions or other cause, the friction sounds may persist even after copious effusion. When the exudate is absorbed the roughened pericardial surfaces again coming into contact may cause a recurrence of the friction.

The Heart.—In many cases the heart is disturbed out of proportion to the severity of the attack. In children the precordial impulse may be diffuse, heaving, and tumultuous, and show visible pulsation in the second and third intercostal spaces due to the auricular contractions; the right ventricle may be dilated and cause pulsation in the costoxiphoid angle. These phenomena frequently occur in protracted cases, in which cardiac dilatation

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is usual and often marked. In the *general circulation*, and especially in the *pulse*, there is sometimes marked disturbance, but it is not characteristic. In some cases the heart is irritable and the pulse very rapid, 120 or more per minute; probably the myocardium is rather extensively involved in these cases. As a rule the respiration is more greatly disturbed than the circulation.

Pericarditis often terminates in the dry stage with absorption of the exudate, or the adhesion of the opposing pericardial surfaces. In most cases, however, *serous effusion* takes place. In this stage the dangers are from two sources: the *abundance of effusion*, and the *degree of degeneration in the myocardium*.

The *fever* may persist, but it is variable; if persistent, it may be due to such accidents as purulent exudation, or inflammation, with or without suppuration in contiguous structures.

The *pain* of the initial stage usually abates gradually, but may be succeeded by a distressing sense of constriction, or of precordial oppression which increases as the exudate accumulates, distends the pericardium, and compresses the heart.

Dyspnœa from the same cause becomes marked, and may occasion much distress, especially if the effusion is rapid. The causes of the dyspnœa are multiple. The distention of the pericardium causing compression of the lungs, especially of the left, interferes with the movements of respiration, and, by pressure, impedes the flow of blood through the heart, especially through the thin-walled auricles.

Venous stasis, chiefly in the pulmonary vessels, occurs and contributes materially to the increase of the dyspnœa which may be marked by paroxysmal attacks and great anguish; in that case the face becomes cyanosed and swollen. When the effusion is large the erect position may give some relief, owing to the liquid collecting in the inferior part of the pericardial sac, thus lessening the pressure on the auricles and great vessels.

The effect of the pressure on the ventricles by the effusion will depend upon the degree of myocarditis existing, as the less the cardiac muscle is injured the more vigorous will be its systole, and, therefore, also its diastole, and the less disturbed by the compression; when it is seriously involved there may be danger of syncope.

Dysphagia may result from pressure of the distended pericardium on the œsophagus; in rare cases, aphonia is caused by pressure on the recurrent laryngeal nerves.

Effusion.—The results obtained by the various modes of examination in this stage of pericarditis are numerous, and of great value in estimating the extent and severity of the lesions.

The results of inspection have already been pointed out. Palpation gives little information. The friction fremitus, if present in the dry stage, will usually have disappeared. The cardiac impulse will be feeble, displaced, and later lost altogether; it will be diffuse if the heart is much altered, but if the dilatation is extreme the heart's contraction may be so feeble as to communicate an impulse only to the small area of the chest over the central part of the heart's surface. In such case the left margin of the heart extends far to the left of the area of impulse, and there may be much difficulty in differentiating dilatation from pericardial effusion. The impulse may reappear on lying down, especially in the prone position, the heart falling

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against the chest wall. The precordial impulse may extend over two or even three intercostal spaces; it may be felt even in the third intercostal space. This increased area of impulse is attributed to the impact of the anterior surface and base of the ventricles; this is rendered possible by the displacement.

The area of precordial dulness, partial and complete, affords important evidence of effusion. According to some observers the presence of one or two ounces of fluid suffices to appreciably alter the area of dulness, but many regard the existence of ten to fifteen ounces as necessary to make the diagnosis of its presence possible. With this and greater quantities, Sibson found the transverse diameter of the dull area at the third costal cartilage, corresponding to the pericardium covering the great vessels, relatively narrow; below this lies the heart, and the left border of the area of dulness is reflected rapidly outward, forming an obtuse angle, sometimes known as Sibson's notch. If this notch can be demonstrated it excludes enlargement of the heart as the cause of the increased area of dulness. The area of dulness may extend to the right of the sternum, appearing first in the fifth intercostal space on account of the accumulation of fluid in the pericardial process that normally extends into this part and becomes distended early in the attack. Dulness in this area has therefore been regarded as diagnostic of effusion (Rotch and Ewart). The extension of dulness being greatest in the fifth intercostal space and lessening as it ascends, converts the comparatively sharp angle between the right margin of precordial dulness and the upper border of liver dulness into a broad obtuse one; this should be of some value in the diagnosis. But Broadbent[1] has, in several instances, found dulness in this area in cases in which postmortem the heart was found dilated and the pericardium adherent, but without the presence of fluid.

Lee[2] points out that acute rheumatism produces, apparently in all cases, dilatation of the left ventricle with a tendency to diffusion and weakening of the impulse of the heart and enfeeblement of the first sound. In the mildest cases of subacute rheumatism the precordial dulness hardly ever fails to reach the nipple line; it usually extends a finger's breadth beyond it and may go farther without any murmur. This dilatation is due, no doubt, to the injurious action on the cardiac muscle of the toxin produced by the rheumatic organisms, frequently also to the actual presence in the heart wall of the organisms themselves.

Rheumatic dilatation of the heart without any pericarditis may give rise to a triangular outline of precordial dulness, with curved sides and its apex upward. When pericarditis is also present a moderate amount of pericardial effusion tends to accumulate behind the dilated heart, in the recumbent position, and does not influence the shape of the dulness. The greatest effect of a moderate pericardial effusion is produced in the second left intercostal space in which a definite lateral increase of the dulness suggests strongly the existence of fluid in the pericardial sac. While a large pericardial effusion, no doubt, extends the precordial dulness farther in all directions, it still remains true that in rheumatic pericarditis the chief factor in the enlargement of the dulness is dilatation of the heart.

[1] *Encyclopedia Medica*, vol. ix, p. 283.
[2] *British Medical Journal*, November 21, 1903, p. 1319.

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The extension of dulness beyond the site of the cardiac impulse has been regarded as quite distinctive of effusion, but such extension of dulness without perceptible impulse may be due to dilatation in which there is marked weakness of the heart's contractions. Ewart has drawn attention to the occurrence of dulness at the base of the left lung close to the spine in cases of large effusion.

Fitz[1] has reported a case of intrapleural lipoma about the size of a newborn child's head, which occupied the anterior and inferior part of the left pleural cavity and obscured the diagnosis of a purulent pericarditis.

Auscultation shows, especially in the dorsal position, enfeeblement, and later, as a rule, disappearance of the friction sound, and weakening of the heart sounds, which to the ear appear distant and flapping. In compression of the lung from large effusion there will be signs simulating pleural effusion; dulness, loss of vocal fremitus and of the vesicular murmur; there may be œgophony, especially in the left mammary region and over the dull area below the left scapula, usually more marked in the dorsal decubitus, but lessening or disappearing in the genupectoral position.

The general circulation is not disturbed so long as the inflammatory changes do not seriously involve the myocardium, or the degree of effusion is not sufficient to interfere much with the diastole of the heart. With the advent of these changes the pulse will be affected, becoming small, irregular, weak, and intermittent; there will be venous fulness, and, from interference with the dilatation of the auricles, venous pulsation in the jugular and other veins.

Stage of Absorption.—The pericardial inflammation may terminate early and the exudate be completely removed, the pericardium being restored to a normal condition; or the lesion may persist for a longer or shorter time and terminate in chronic pericarditis. In many cases the exudate is rapidly absorbed, and during this process the physical signs of the first stage may all return, but in the reversed order; lessening in area of dulness, increase of the heart sounds and impulse, and recurrence of the friction sound. Such signs as persist will be due to myocardial changes and adhesion of the pericardial surfaces.

The Forms of Acute Pericarditis.—*Pericarditis Sicca.*—In many cases pericarditis remains dry throughout its whole course; it may be localized or general. It usually produces little disturbance; there is slight pain and some tenderness at points along the course of the phrenic nerve as already described. If carefully and frequently searched for the friction sound will usually be heard, but it lasts only a short time.

Serofibrinous Pericarditis.—This is the common form; its first stage presents the same symptoms as the dry form. It occurs frequently in rheumatism and co-exists quite often with endocarditis. It may be a primary lesion, as after exposure to chill, or from pneumococcic infection, as well as secondary, especially in the course of pleurisy, pneumonia, and Bright's disease.

Purulent Pericarditis.—This form may be a primary lesion, but more frequently it occurs in the course of pyogenic infectious diseases, or as a secondary streptococcic or staphylococcic infection in debilitated subjects. A serofibrous effusion may become purulent; a non-aseptic puncture or

[1] *Transactions of the Association of American Physicians*, vol. xx, p. 57.

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aspiration would precipitate such a change in the exudate. In addition to the ordinary signs of pericardial effusion there is protracted fever of a septic character, emaciation, free perspiration, a muddy appearance of the skin, and great prostration. The pulse and heart's action are weak on account of the infection of the myocardium. The course is usually short, it may be only two or three days in terminating fatally; recovery is rare. Free evacuation and drainage may, however, give greatly improved results in the future.

Hemorrhagic Pericarditis.—This form of pericarditis presents no especial phenomena to indicate the character of the effusion. It may occur in the course of cardiac affections and injuries, Bright's disease, carcinoma, tuberculosis, alcoholism, and in the aged. In most cases the exudate is a blood-stained serum in which leukocytes are moderately numerous; the fibrinous exudate is usually scant. The pericardium is deeply stained with blood pigment. The red blood corpuscles are at first intact, but soon break down, and the coloring matter set free is diffused in the serum. Small extravasations into the pericardium are frequently found. In the hemorrhagic eruptions of fevers and scurvy the prominent feature is the cardiac weakness with collapse and syncope; sudden death is usual. If the hemorrhage is abundant, there will be phenomena analogous to those in other free internal hemorrhages; vertigo, oppression, cold sweat, small, weak pulse, faintness, cold extremities, and death more or less sudden.

Chronic Pericarditis.—The chronic affection is ordinarily the sequence of an acute pericarditis in which recovery has been arrested in the course of the absorption of the exudate, but there is no definite time at which the disease merits the name of chronic pericarditis. In certain cases the affection develops so imperceptibly as to merit the appellation when first discovered, particularly in the aged, in chronic nephritis, in the tuberculous, alcoholics, and the debilitated. In the cases of pericarditis of insidious development, the exudate may be large, often purulent or hemorrhagic, and cause dyspnœa with precordial oppression. Its existence may be recognized only after long duration by the occurrence of subacute attacks.

When chronic pericarditis succeeds the acute form it is characterized by the persistence of the physical signs; stationary or gradually diminishing effusion, which may increase from time to time with a return of the acute symptoms, and signs of increasing myocardial degeneration, especially in the circulation becoming more and more defective with the usual symptoms resulting from such a condition. The pericardium may become in time adherent over its whole surface and the case thus terminate in *adherent pericardium.*

In rare cases the various symptoms gradually abate, the exudate is absorbed and complete recovery takes place.

Course, Duration, Termination.—It is impossible to give more than approximately the duration of acute pericarditis as it presents multiple forms, very variable intensity, and, in its general course, is much affected by the infectious disease with which it is associated. In the adult it is usually acute and the symptoms severe; in children it is more often subacute and insidious in its development, and frequently runs a long course, terminating in adhesion of the two layers of the pericardium.

In mild cases of dry pericarditis, even although the general symptoms are marked, the friction rub may disappear in a few days, and convalescence may be rapid. Even with moderate serofibrinous exudation the recovery

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may be as rapid, but this is rare. In a recent case, with very great exudation, apparently fibrinous absorption was almost complete within ten days.

In very severe cases death may take place within a few days after the onset, but this is unusual, and generally due to the associated diseases, such as pneumonia. In such cases there is serious implication of the wall of the heart causing much dilatation with great increase in the area of precordial dulness, high temperature, rapid, weak pulse, and much prostration. These phenomena are not due to the pericarditis but to the myocarditis; at the autopsy there is found a moderate exudate of lymph on the pericardium giving rise to a shaggy appearance of its surface, and the heart is greatly dilated and its structure in a state of extreme, acute degeneration.

The onset of pericarditis in rheumatic children is usually insidious, and when first examined both apical systolic murmurs and friction sound may be present. The friction rub may persist for days or even weeks, the area of precordial dulness in the meantime becoming greatly enlarged from cardiac dilatation. Pericardial adhesion gradually takes place and the heart never regains its normal size and vigor. After recovery the child remains weakly, pale, and short of breath, and the heart is permanently crippled on account of the pericardial adhesions, and the permanent changes in the myocardium resulting from the inflammation and the valvular affections which frequently co-exist. In these cases, as well as in those of protracted or repeated pericarditis, the heart becomes extremely dilated and the changes resulting from marked defect in circulation supervene—enlargement of the liver, bronchitis, ascites, and, later, general dropsy. It is a question whether myocardial degeneration is secondary to the pericarditis, or is due to a simultaneous infection.

Diagnosis.—The existence of pericarditis is very frequently overlooked. Its course in many cases is so insidious and the signs so indefinite that its existence is not suspected, and a careful examination is therefore not made; and also because it is so often associated with other diseases, especially pneumonia, which overshadow its symptoms and frequently so obscure it as to make a diagnosis impossible, or, at most, only probable. Such symptoms as pain in the precordium, the tender points along the course of the phrenic nerve, already referred to, the quickened respiration, anxious countenance, and venous stasis may indicate its occurrence, but then most of these symptoms may be present also in pneumonia, in diaphragmatic pleurisy, in endocarditis, and especially in myocarditis, to the co-existence of which they are probably in the main due in pericarditis.

The one physical sign that is practically characteristic is the friction rub, and, without it in the absence of effusion, a diagnosis is impossible. There are many cases, however, in which it is not found; it may be slight, last only a few hours, and disappear before an examination is made, or occur only between examinations. But once distinctly heard it can scarcely be confounded with anything else. Difficulty may arise in cases of dry pleurisy affecting the pleura in immediate contact with the pericardium; in such a case the cardiac movements may cause a pleural friction rub and as it is synchronous with the movements of the heart, it closely simulates pericardial friction. The pleuritic rub is more modified by respiratory movements, and is audible only over the left border of the heart and not over the sternum or base of the heart. Furthermore, a pleurisy is seldom confined to this area, but extends outward over the lung into the axilla.

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It is also usually intensified by deep expiration, and weakened or quite lost in inspiration. In pericardial cases the distinctive character of the rub is probably usually accentuated in inspiration.

In mild subacute attacks of pericarditis, especially in children, the onset is so insidious that the disease may exist for some days and the heart have suffered serious damage before the child is considered to be seriously ill, and even then it is only after a careful examination, in which the signs of pericarditis are sought for, that the actual condition is recognized.

Endocardial murmurs are usually easily distinguished from the pericardial friction rub, and the diagnosis presents no difficulty; but in the ill-defined cases of either disease, and in the cases in which they co-exist, the differentiation is quite frequently impossible. Endocardial sounds have a point of maximum intensity from which they are propagated to some distance, while the pericardial sounds are usually definitely localized in a very narrow area around the point of production. Respiration and the posture of the patient, as a rule, greatly alter and often obliterate the pericardial friction sound; usually they have much less influence on endocardial murmurs. But in many cases posture greatly alters the endocardial murmurs; they may be loud and distinct in the recumbent position, and become weak or even disappear in the erect, or vice versa. Endocardial murmurs are not affected by pressure with the stethoscope; they are not superficial, and they have a distinct relationship to the sounds of the heart which they may replace wholly or in part.

The diagnosis of *pericardial effusion* from cardiac dilatation frequently presents great difficulties. Effusion is indicated by dulness extending beyond the point of cardiac impulse, to the right of the sternum, especially in the fifth intercostal space, and upward above the third left costal cartilage. It occurs most rapidly and extensively in the severe and acute cases, and is marked also in the late stage of subacute and recurrent ones. It is greatest in children, in whom also it is more easily demonstrated on account of the thinness of the chest wall and absence of emphysema, and in them it may cause bulging of the precordial region. The existence of Sibson's obtuse notch, already described, if demonstrable, is of much value. The boundary of the dulness of effusion is usually more abrupt than that of cardiac enlargement, and the transition from the flat note over the effusion to the resonant one over the lung is usually sudden. As the effusion increases the area of dulness tends to become pyriform, and it extends upward toward the clavicle farther than cardiac dulness. Change in position and shape of the dulness with change of position of the patient is a valuable sign if it can be definitely made out.

Dulness in the right fifth intercostal space has been regarded as evidence of effusion (Rotch, Ewart), but Broadbent has found it postmortem in several cases in which there was no fluid, but only a dilated heart and adherent pericardium. Shifting dulness in this space is occasionally found and is a valuable sign.

Increasing weakness of the cardiac impulse until it finally is completely lost, with growing enfeeblement of the sounds of the heart, and, at the same time, rapid increase in the area of precordial dulness, are strongly indicative of pericardial effusion. With large effusion there is usually marked increase of precordial oppression, fulness of the veins of the neck, cyanosis, a small irregularly feeble pulse, distressing dyspnœa, and even orthopnœa.

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In cardiac dilatation the dulness is triangular, the long diameter being transverse, owing to displacement outward of the left border of the heart, and the dulness seldom if ever extends upward above the third costal cartilage. The heart sounds are dull, the impulse feeble but ordinarily perceptible, and there is often the *bruit de galop;* the pulse is feeble and irregular. The evolution of the symptoms is usually less rapid than with those caused by massive effusion.

Notwithstanding these differences, there are many cases in which a differentiation of dilatation from effusion is quite impossible. In pericarditis, with only plastic exudate, the myocardium may be so profoundly involved that great dilatation develops rapidly, the sounds become very indistinct, the impact of the heart against the chest wall barely perceptible, and that only at its most prominent part and not at its left border, so that the dulness extends well to the left of the impulse and to the right of the sternum. The general symptoms become very marked, such as urgent dyspnœa; anxious, pallid facies; turgid, pulsating veins at the base of the neck; cyanosis; small, feeble pulse, and profuse perspiration. Error in diagnosis has often led the most experienced observers to perform aspiration for the removal of pericardial fluid that did not exist; they have punctured the right ventricle on several occasions, but fortunately without any injurious effect. The cardiac reflex described by Abrams,[1] if it can be obtained, will be a positive indication of dilatation, but it is probably too feeble in most cases of such marked dilatation to be perceptible.

Even paracentesis does not necessarily determine the presence or absence of fluid in the pericardium; the heart may lie in front of the fluid and prevent access to it. Shattuck[2] met with several interesting cases apparently of this nature. In a young man, under the care of the writer, suffering from a very severe rheumatic pericarditis, apparently with much effusion, precordial dulness extended upward to the second rib, to the left a little beyond the anterior axillary line, and to the right beyond the sternum 5 cm. in the fifth, and 3 cm. in the fourth intercostal space. He had frequent severe attacks of dyspnœa. Aspiration was tried in the left costoxiphoid angle, in the right fifth intercostal space, and in the left fifth intercostal space, first close to the sternum, and then an inch internal to the left margin of precordial dulness, but all were negative, although the needle entered the pericardial cavity in each instance; it came into contact with the heart only in the first and the last two instances, after passing through an exudate from half an inch to an inch in thickness. There was marked dulness and loud blowing breathing at the angle of the left scapula, over the area described by Ewart as indicative of massive pericardial effusion. Improvement began a few days later, the area of precordial dulness diminished and the blowing breathing heard posteriorly rapidly disappeared. It seems probable that all the signs were due to extreme dilatation of the heart and copious plastic exudate. This view is supported by the rapid disappearance of the dulness posteriorly, as the heart contracted after digitalis was given freely.

Effusion into the left pleura may simulate pericardial effusion, and vice versa, especially if the pleural fluid is encysted in the neighborhood of the

[1] *Medical Record*, New York, January, 1901.
[2] *Transactions of the Association of American Physicians*, 1897, vol. xii, p. 183.

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pericardium. The shape of the dull area, the condition of the lung, the position and character of the cardiac impulse, and the tone of the heart sounds should suffice to differentiate the two conditions. The co-existence of both pleural and pericardial effusions may be more perplexing, but the signs peculiar to each are sufficient, as a rule, to guide to a correct diagnosis.

Affections accompanied with induration of the lung overlapping the heart, tumors in the mediastinum, and aneurism of the aorta, increase the area of precordial dulness, but are distinguished from pericardial effusion by the form and topography of the dull area, and other symptoms and signs of the conditions.

In the determination of the *nature* of the effusion, the physical signs afford no assistance; the general phenomena, such as the course of the temperature, the general condition of the patient, the co-existing affections, and, above all, the cause of the disease, may furnish indications sufficient to decide whether the exudate is serofibrinous, purulent, or hemorrhagic. But in the majority of cases a positive diagnosis can only be made by withdrawing some of the fluid. The character of the infection on which the pericarditis depends does not necessarily determine the nature of the exudate. Thus, in tuberculous cases the exudate may be serous or hemorrhagic; in rheumatic cases it is usually serous, but may be purulent; and in septic cases, although usually purulent, it may be serous.

Prognosis.—"Pericarditis, like other acute inflammations occurring in an otherwise healthy individual, may be expected to run a favorable course if not unduly treated" (Balfour).

The prognosis of simple, acute pericarditis without complications is favorable; the graver prognosis of the older authors is to be attributed to their having included the more serious lesions of the heart itself in their estimate of pericarditis. As the pericardium is not a vital structure, its inflammation can be dangerous only as (1) it affords a large surface for absorption of toxic products; (2) the inflammation extends to the heart muscle; and (3) the effusion, by its volume, compresses the heart and impedes its diastole. Of these dangers the second is much the most frequent and grave, and it is this that makes pericarditis the most frequent cause of death in acute rheumatic fever.

In most severe cases the signs of dilatation and disturbed action of the heart occur so early that infection of its tissue must take place simultaneously with, or very soon after, that of the pericardium. In the majority of cases there is recovery from the pericarditis, but the liability to relapse and damage of the heart muscle, and to adhesions of the pericardial surfaces, renders the ultimate prognosis in many cases far from favorable. The prognosis, therefore, depends chiefly on the extent to which the cardiac tissue is involved, and this is fairly indicated by the degree of dilatation and disturbance of the action of the heart. As in endocarditis, the younger the child the greater is the liability to pericardial infection in rheumatism, also to invasion of the heart muscle, so that age greatly influences the prognosis. In advanced age the outlook is also grave.

Much depends on the associated diseases. The influence of the myocardial lesions has already been referred to. Acute endocarditis and pneumonia add greatly to the danger, chiefly from the greater liability to degeneration of the heart muscle. The association of chronic nephritis also adds greatly to the gravity, as does also tuberculosis as the exciting cause of the

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pericarditis. The nature of the effusion has much significance, the prognosis being much more grave when it is purulent or hemorrhagic than if it is serous.

Treatment.—The therapeutic indications vary according to the form of pericarditis, the period of its evolution, the chief phenomena presented, and the accidents which complicate its course. It is important to appreciate the fact that the danger arising from pericarditis is rarely due to the inflammation of the serous membrane itself, but first, to the pressure of the accumulated effusion hampering the action of the heart, only an occasional danger, and, secondly and chiefly, to the occurrence of inflammation in the wall of the heart itself, probably from simultaneous infection rather than from extension from the pericardium.

The treatment may be reduced to two general principles: to combat the inflammation of the pericardium, and to prevent the failure of the heart.

In counteracting the inflammatory process, especially in acute pericarditis, local applications to the precordial region are of chief importance. Various revulsants have been long in use, such as local bleeding, leeching, hot applications, sinapisms, and a series of small blisters. These measures usually quickly relieve the thoracic pains and distress. The application of cold over the precordial area by means of compresses or icebags has become increasingly general in recent years. It usually relieves pain and steadies the action of the heart so that the application is not only well borne but comforting to the patient. The effect of cold is probably to stimulate reflexly the vasomotor nerves of the pericardium, causing contraction of the vessels and lessening of the blood supply; this is similar to the effect of cold applied to the chest on the vessels of the bronchial mucous membrane, as shown by Brunton.

In the case of the bronchial mucous membrane, if the cold application is too long continued, vasomotor paresis occurs, and the vessels dilate and the membrane becomes turgid; but the repeated application of cold after shorter or longer intervals, during which the skin has been warmed, stimulates the contraction of the vessels and consequently lessens the congestion of the mucous membrane. These observations must be true of the pericardium also, so that the frequent application of cold to the precordium will probably give the best results in checking the inflammation. In urgent cases better results are sometimes obtained by the application of a cold compress for a few minutes, after which it is removed and the surface warmed by hot fomentation, and then the cold compress is again applied, to be again followed by the hot fomentation. These alternations of cold and heat may be continued for an hour or more and repeated several times a day. In place of the compresses, Leiter's tubes may be used. The existence of aortic disease is said to be a contra-indication to the use of cold applications, probably because they stimulate the heart and raise the blood pressure; it is probably a groundless fear.

The repeated application of a series of small blisters has been strongly advocated by some writers, especially by Caton. The application of two or three leeches to the precordium has proved useful in many cases, especially when there is pain. Antiphlogistics and general resolvents, such as mercurials and tartarated antimony, once so freely used, have fallen into disrepute, because of doubtful value and not exempt from danger.

The salicylates, which usually have such marked beneficial effect in the

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acute articular rheumatism of adults, are generally regarded as having little, if any, beneficial effect on the inflammation of the heart or its membranes, endocardial or pericardial, and as liable to cause dangerous depression of the heart if given freely, especially in pericarditis. Lee strongly combats this. He attributes the cardiac weakness and dilatation to the effect of the toxin of acute rheumatism on the heart muscle, and not to the salicylate. There is much truth in this contention; but it is also apparently true, unfortunately, that once the cardiac structures are infected the salicylates have little influence in checking the infection. The same observation is nearly as true regarding joint infections. In both cases the salicylates, if given before infection of the cardiac and joint structures, respectively, and in sufficient doses, will probably prevent the infection or at least lessen its virulence. Care should be taken that the salicylate of soda is pure; about 20-grain (1.3 gm.) doses with an equivalent or even double the quantity of potassium or sodium bicarbonate should be given every two hours to the adult until the fever and pain are moderated, when the intervals may be increased to four hours, and, after a few days, the dose gradually reduced.

If the local applications of cold and heat fail to give relief to the pain, restlessness, and dyspnœa, opium or morphine may be given with much benefit. During the acute stage if stimulants are required, ammonia, alcohol, caffeine, strychnine, and strophanthus should be given, and not digitalis, lest it cause too great a strain on the injured heart by increasing the blood pressure through contraction of the arterioles. Quinine, given in an effervescent draught of bicarbonate of soda of potash, is a useful remedy. If the depression is marked and there is a tendency to syncope, caffeine subcutaneously usually proves an efficient cardiac stimulant. The pure alkaloid is the most reliable, and with the addition of 1 or 2 grains of salicylate of soda, as much as 5 grains (0.3 gm.) can be dissolved in a hypodermic syringeful of water; the injection may be repeated frequently in urgent cases. It is often more efficacious than even large doses of digitalis, and is free from danger; but in some cases it causes nervousness and prevents sleep. Diuretin (theobromine salicylate) is an excellent cardiac stimulant and diuretic in many cases; it may be given in about 15-grain (1.0 gm.) doses three or four times daily. Theocin, in doses of 3 to 8 grains (0.2 to 0.5 gm.), often proves a better diuretic. Atropine is sometimes of value; it should be given freely enough to cause a slight physiological effect. Potassium iodide has been recommended, but its usefulness is doubtful.

If the dyspnœa is the result of pulmonary congestion and does not yield to local applications to the precordium and to internal stimulation, recourse should be had to venesection. In any condition attended by overstrain and distention of the right ventricle, venesection, even if copious, is not dangerous. The more quickly the blood flows the greater will be the fall of pressure in the right ventricle, and therefore the greater its relief. If the loss of blood is deemed undesirable an equal quantity of physiological salt solution may be given subcutaneously to replace the volume of blood lost.

In severe cases of rheumatic cardiac inflammation in children, nothing seems to have any influence on the progress of the disease, the course of which is usually rapidly progressive to a fatal termination. It is therefore important that children showing any indications of rheumatism should be promptly put to bed so as to be quiet and warm. The heart should be care-

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fully examined from day to day, so that the most effective treatment may be resorted to at once on the first signs of involvement of any of the structures of the heart. The salicylates should be given freely, with large doses of bicarbonate of soda; children bear the drug well.

Pericardial effusion, when established, requires good judgment in its treatment. If moderate and the heart shows no signs of embarrassment, no special treatment is required, since, as a rule, it soon becomes absorbed. The patient should be placed in bed, so as to relieve the heart of work as far as possible. If the effusion persists, absorption may be aided by repeated small blisters to the precordium, by diuretics, and saline purgatives. In all cases, common salt should be excluded from the diet, which should also contain little liquid.

If these measures have little effect, and in all cases of large effusion, especially if there are signs of cardiac disturbance, *paracentesis* should be done without undue delay, as death from syncope is liable to occur. It should be borne in mind, however, that the cardiac embarrassment is, in most cases, due chiefly to disease of the myocardium and the consequent dilatation, and, usually only slightly, probably in most cases not at all, to the pressure of the effusion. In many cases, therefore, little and only temporary relief results from paracentesis.

Paracentesis of the pericardium was first proposed in 1649 by Riolan, and afterward by Senac in 1794. The operation was very slow in being recognized as justifiable, not to say advisable; as late as 1870, Billroth characterized it as a prostitution of surgical skill. Various sites are recommended for puncture, the fourth or fifth left intercostal space near the sternum being the ones most often selected; next to these in the same spaces outside the nipple line and within the line of flatness on percussion. A third point, and, if the diaphragm is depressed, probably the best, is high in the angle between the xiphoid cartilage and the left costal margin, the needle being directed backward until it has penetrated as far as the posterior surface of the costal cartilage and then turned sharply upward and to the left behind it; it should at once enter the cavity of the pericardium. The failure to obtain fluid does not necessarily prove its absence. A "dry tap" may be due to the plugging of the needle as it passes through the plastic exudate, to plugging by thick flakes of fibrinous exudate, or failure to enter the cavity containing the fluid.

The fifth right interspace, about an inch from the sternum, has been selected when this area is decidedly flat; it is probably not so uniformly satisfactory as the other points. An exploratory puncture with a hypodermic syringe is advisable to demonstrate the presence of fluid; but it is important to remember that the fluid may not be reached by the hypodermic needle if there is much fibrinous deposit on the pericardium. A small aspirating needle should be used, the greatest care being taken to ensure an aseptic operation. If a small incision be made through the skin the needle can be inserted much more easily, as it is not then grasped by the elastic subcutaneous tissue. After the aspiration the wound should be sealed by a suitable dressing.

Re-accumulations of effusion will necessitate repetition of the aspiration. In some cases as many as ten aspirations have been made, with ultimate recovery as far as the pericardial effusion is concerned. Charton punctured thirteen times in a man aged forty-six years, for hemorrhagic effusion, but a final relapse was followed by death.

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For purulent exudations free drainage will usually be required just as in empyema, especially in cases of general sepsis. Most cases are fatal because of incurable associated conditions. The incision is usually made in the fifth left intercostal space close to the sternum. If there is insufficient room for drainage a semilunar portion of the costal cartilage may be cut away, also a portion of the margin of the sternum. At this point the pericardium is easily reached by carefully dissecting down to it, and there is no danger of wounding the pleura.

The injections of iodine solutions or antiseptic fluids are seldom required, and probably never beneficial; but they may be injurious, as they so often are in empyema of the pleura.

In *chronic pericarditis* medication is ordinarily quite powerless for good. Some benefit may result from prolonged use of vasomotor stimulants like cold and heat, or such revulsants as blisters, etc., to the precordial region, and from the employment of tonics such as quinine, iron and arsenic, and of good food and fresh air, especially in new and favorable surroundings. Potassium iodide may be employed with benefit in some cases as an alterative. However, it is usually the degenerative changes in the myocardium that demand most attention.

The persistence and recurrences of effusion are to be met by dry salt-free diet, diuretics, repeated hydragogue purgatives, and, in suitable cases, paracentesis.

The *diet* in pericardial affections, in general, should be generous, as the tendency in these diseases is to degeneration of the wall of the heart from infection and insufficient nourishment. If the veins become unduly distended from defective circulation the diet should be "dry," in order to lessen the fluid to be absorbed from the intestines. The amount of sodium chloride taken should be reduced to a minimum if there is any sign of œdema, so as to reduce the tendency to osmosis into the connective tissues; it may have to be omitted even in the preparation of the food.

ADHERENT PERICARDIUM.

Synonyms.—Symphyse cardiaque; synechia seu concretio pericardii.

Definition.—Adherent pericardium is, properly speaking, only the adhesion of the two layers of the pericardium resulting from divers forms of pericarditis, and, therefore, neither a disease nor an affection. Nevertheless, it presents such special clinical signs and has associated with it such intra- and extrapericardial lesions that it merits special description.

History.—The condition was known to Galen and most ancient authors, and regarded by them as congenital absence of the pericardium. It was not until the sixteenth century that its inflammatory origin was first recognized. From that time onward to the present many observers in France, Britain, and Germany have added observation to observation until the present status of knowledge of the subject has been attained.

Etiology.—All varieties of inflammation of the pericardium, acute or chronic, may bring about the formation of adhesions and obliteration of the cavity. Hence, the causes of this final morbid change are as various as those of pericarditis. The chief causes are rheumatism, pleuropulmonary affections, and tuberculosis. The adhesion may take place in the course of dry pericarditis, and after the absorption of effusion, especially when the

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affection tends to chronicity; also in cases that present a number of successive subacute attacks extending over years. In the latter the inflammation may extend to the mediastinum and ultimately form a *chronic fibrous mediastino-pericarditis.*

In some cases the process begins in the mediastinum as in acute or chronic inflammation due to disease of the bronchial glands, malignant tumors, tuberculosis of the lungs or pleura, pneumonia, aneurism of the transverse aorta, or from trauma, the infection extending to the pericardium and producing a slowly spreading inflammation.

It occurs in early oftener than in later life. Of 22 cases collected by Harris, 9 occurred before eighteen years of age, and only 2 after thirty. It has been met with in infants and even in the newborn, showing the possibility of the occurrence of pericardial inflammation in intra-uterine life. Its frequency, as reported by different authors, varies greatly according as partial or complete adhesion is considered; statistics are, therefore, not satisfactory. Thus, Leudet, in a large number of autopsies, found adhesions, partial in 5 per cent. and complete in 2½ per cent. of all the cases. At the Berlin Charité the records show 156 cases of adhesions of all kinds in 324 cases of pericarditis.

Special Pathology.—This comprehends the study, first, of the pericardial adhesions; second, lesions in the mediastinum from extension of an infective process which sometimes extends to the serous membranes on both sides of the diaphragm; and, third, the alterations in the heart itself and their consequences.

1. **Adhesions in the Pericardium.**—These may be partial or general. When adhesions form after pericarditis they begin between the auricles and the parietal pericardium where the great vessels pierce the latter to enter the cavity; partial adhesions occur only rarely in the region of the apex. The adhesions may consist of the close attachment of various-sized plaques of the two serous surfaces, or the connection may be by bands or strands of connective tissue of varying length, shapes, and sizes, and more or less vascularized. The adhesions may be so extensive and so arranged as to form loculi of various dimensions in which exudate may be encysted. The effect of the adhesions on the heart's action will vary with their size and length, and the firmness of their attachment to the neighboring structures.

General adhesion is rare, and often more apparent than real, for the membranes can, in most cases, be separated easily, yet these are cases of true obliteration of the pericardial cavity.

The adhesions, partial or general, are at first soft and easily broken down; in time as the granulation tissue becomes organized, they are formed of firm, resistant, fibrous tissue. The two layers of serous membrane may be so intimately united that in the fibrous layer formed it is impossible to find a trace of the original membrane. The thickness of the covering of the heart thus formed is, therefore, very variable; thick deposits are especially liable to occur in tuberculous cases. The greater part of the deposit is usually formed by the visceral layer. The thickness may exceed even that of the cardiac wall, which may be difficult to separate from the fibrous mass. In occasional cases the adhesions undergo cartilaginous or calcareous change. The calcareous change usually follows a purulent exudate which has been partly absorbed and then certified, forming calcareous, isolated plates or a more or less complete case investing the heart.

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2. **Lesions of Neighboring Structures.**—These are frequent and consist of bands in the mediastinum which form adhesions joining the fibrous pericardium to the thoracic wall and the mediastinal pleura in front, the great vessels, œsophagus and spine behind, and to the central aponeurosis of the diaphragm below. They are the result of chronic recurrent inflammation, develop slowly and are very various in extent. In occasional cases all the loose mediastinal cellular tissue is replaced by a dense, fibrous mass enveloping all the organs in the mediastinum, the whole being intimately attached to the thoracic wall, the pleuræ, the spine, and the diaphragm.

3. **State of the Heart.**—This rarely remains normal when surrounded by such multiple and diverse lesions, as they must interfere more or less with its movements. Keith[1] points out that the heart is normally, firmly fixed to the roots of the lungs by fibrous prolongations of the pericardium carried into them on the pulmonary veins and arteries in the process of development. He quotes John Hunter's morphological law that the heart is always attached to the organs of respiration and follows the movements of these organs.

It is generally agreed that in cases in which the adhesions are few in number, and not tense, they have little, if any, influence on the state of the heart, which has been found normal in a large number of cases. But if the pericardial adhesions are extensive and firm, and the myocardium has been infected simultaneously with the pericardium, important changes will have occurred in the heart itself. These changes are due partly to interference with the heart's action by the adhesions, and partly to the degenerative processes resulting from the infection of the wall of the heart. Many observers have found the heart enlarged from hypertrophy and dilatation, while others regard atrophy as the more usual change. There can scarcely be a doubt that the former change is the usual one, because in these severe cases of pericarditis the tissue of the heart can scarcely escape infection, and this will injure its tissue and weaken its power so that dilatation should occur before adhesions and fibrous bands have become sufficiently firm to prevent the dilatation. Later, hypertrophy will follow from the increased labor arising from the interference with its activity by the adhesions and bands unless their contraction interferes with the blood supply to the cardiac walls. In 19 cases, Sibson found considerable enlargement in 12, slight enlargement in 5, and in only 2 was the heart of normal size.

If the myocardium has been little injured by the infection, the conditions are favorable for hypertrophy, especially in the absence of valvular lesions; the hypertrophic changes will be most marked in young persons. In general debility from any cause, and especially in the cachectic and the tuberculous, the conditions are not favorable for hypertrophy, and a greater or less degree of atrophy is frequent.

Valvular lesions are frequent, as endocarditis is often caused by the same infection as the pericarditis, which, however, may be secondary to chronic endocarditis.

In rare cases an excessive degree of new, fibrous tissue has been formed about the roots of the great vessels, and its subsequent contraction has led to narrowing, or even complete occlusion, of one or more of them. The vena cava, superior or inferior, is most often affected, but the pulmonary artery or the aorta may also be involved. The secondary changes caused

[1] *Lancet*, 1904, vol. i, p. 558.

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by these vascular constrictions are widespread and vary according to the vessel or vessels affected.

In some cases of obliteration of the pericardial sac, various secondary changes not limited to the heart develop. The most remarkable of these are widespread proliferative inflammatory thickening of the various serous membranes, multiple serositis or hyaloserositis or polyorrhymenitis, and induration of various organs, especially of the liver, due to proliferation of its capsule and obstruction to its circulation. The symptoms so closely resemble those of ordinary cirrhosis of the liver that the term *"pericarditic pseudo-cirrhosis of the liver"* has been applied to it or, more frequently, "chronic universal perihepatitis." Chronic peritonitis and chronic pleuritis often co-exist, the infection apparently spreading from the diaphragm in both directions. There is marked thickening of the peritoneum, especially over the liver, where it is often irregular, producing a fenestrated appearance, or "iced liver," the "Zuckergussleber" (Curschmann). Chronic changes in the lungs are also often found, partly due to the obstruction to the circulation from the endopericardial affection, and partly to retraction of the lungs from pleuro-pericardial adhesions. Much has been written on this remarkable condition by various writers, especially by Rolleston in England, Nicholls in Canada, and Kelly in the United States.

Symptoms.—Most extensive adhesion of the pericardial surfaces may occur without causing any symptoms, hence the frequency with which the condition, unsuspected during life, is found at the autopsy. In a number of cases there is a history of long-continued and increasing disturbance of circulation and respiration which is usually attributed to associated valvular defects. In another group of cases, chiefly of chronic adhesive mediastinopericarditis, the symptoms simulate those of hepatic cirrhosis, ascites being marked and requiring repeated tappings.

Laennec, although slow to recognize the signs of pericarditis, had a clear perception of the importance to be attached to this affection. After pointing out that in certain cases acute pericarditis is a local disease of little gravity, he says that, "after having encountered a number of cases of the kind, that adhesion of the heart to the pericardium in no way interferes with the exercise of its function." The frequency with which simple adhesion of the layers of the pericardium is met with without material injury to the heart, even when the sac is completely obliterated, shows the correctness of his opinion. The pericardium is so loosely attached to the surrounding structures that simple adhesion cannot hamper it materially. The disturbances to circulation so frequently existing are to be accounted for chiefly by the associated conditions. In the order of their importance they are: affections of the myocardium usually resulting from the same infection and occurring simultaneously with that of the pericardium; valvular affections, often the result of endocarditis occurring also simultaneously with the pericarditis; chronic fibrous mediastinopericarditis; and massive fibrous thickening in and between the layers of the pericardium, with, in rare cases, the deposit of calcareous concretions. Other causes, such as pressure of fibrous bands on the great vessels and multiple hyalositis, are of rare occurrence.

With so many associated conditions, each of which may cause the gravest disturbances, it follows that cases of adherent pericarditis must present great variety of phenomena.

The general symptoms are those of circulatory disturbance and insuffi-

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ciency, but they are not pathognomonic of pericardial adhesion; palpitation, tumultuous heart action, precordial oppression, dyspnœa, anxiety, a tendency to syncope, cyanosis, etc. All these indicate disturbed function or insufficiency of the myocardium, whether arising from changes following inflammatory processes or other causes. There is no doubt that these symptoms, especially the dyspnœa and cyanosis, are largely dependent on the disturbance of respiration, owing to interference with the movements of the diaphragm by the mediastinal adhesions, as pointed out by Wenckebach.[1]

Physical Signs.—Systolic, rhythmical retraction in the lower part of the precordial area, when present, is the most important sign of adherent pericardium. This systolic retraction may be confined to one or more intercostal spaces in the area of cardiac impulse, or be more widely distributed, affecting several spaces and sometimes the epigastrium, or, if still more forcible, the costal cartilages and even the lower end of the sternum may be drawn inward. When limited to the intercostal spaces about the cardiac impulse, the sign is not of material value, as it is sometimes observed in connection with other lesions, as in pleural adhesion at the margin of the left lung without any affection of the pericardium, and it occurs occasionally without adhesions of any kind.

The retraction of the costal cartilages, and sometimes of the sternum, is a sign of much greater value, but yet not pathognomonic. It is apparently due to the strong adhesion of the pericardium to the inner surface of the thoracic wall on the one hand and to the heart on the other, so that during the systolic contraction of the heart the chest wall is drawn inward. A similar phenomenon, however, sometimes occurs without adhesion of the pericardium to the chest wall. Intimate adherence of the heart to the diaphragm alone has been observed to cause retraction of the lower precordial region by traction on the attachments of that structure to the thoracic wall.

Depression in the precordial region may also be observed when cardiac adhesions offer an obstacle to the normal movements of the heart at the base and to the left. In such a case, especially if the base of the heart is fixed, the retraction and elevation of the point of the heart in systole and the pressure of the air cause depression of the intercostal spaces. James MacKenzie[2] points out that, in certain cases of dilatation of the right heart, nearly the whole anterior aspect of the heart is composed of the right auricle and ventricle, so that the latter is the part in contact with the chest. During systole the ventricle is diminished in size and drawn inward, and the tissues of the chest wall recede with it; they are forced outward again in diastole, partly by their own elasticity and partly by the pressure of the dilating heart. Pleuro-pericardial or pleuro-costal adhesions often exist, and by preventing expansion of the process of the left lung that overlaps the heart, they usually increase the precordial recession. Such pleuro-costal adhesion is usually associated with some lessening of the tympanitic semilunar space of Traube.

Marked undulatory movement is sometimes observed over the precordial area beginning above and to the right and extending downward and to the left; it is a kind of rolling movement and may sometimes be observed also in the epigastrium. It must be remembered, however, that undulatory movements may be produced in dilatation of the heart by irregularity in the

[1] *British Medical Journal*, 1907, vol. i, p. 63.
[2] *The Study of the Pulse and the Movements of the Heart*, 1902, p. 39.

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contractions of the various chambers without there being any adhesion of the pericardium. The movements in this case should be less regular and more subject to alteration by rest and treatment than those due to adhesions.

Immobility of the diaphragm in its central part, or decided limitation of its movements, as shown by deficient epigastric movement, or by *x*-ray examination, may be due to adhesion between the heart and diaphragm; it is more marked if the adhesions also include the chest wall.

Systolic retraction of the tenth and eleventh intercostal spaces below the scapula—Broadbent's sign—is regarded as evidence of extensive adhesions between the heart and diaphragm. It is occasionally seen on the right side as well as on the left. Its occurrence is attributed to the powerful traction of a greatly hypertrophied heart on the diaphragm.

Diastolic collapse of the veins of the neck was regarded by Friedreich as a sign of much importance. Broadbent has observed systolic collapse in the superficial veins on the anterior surface of the chest; he attributed it to the traction of fibers extending from the pericardium to the internal mammary veins dragging in and opening them during systole, and obstructing and causing sudden distention of these veins during diastole.

Kussmaul's sign, or swelling of the cervical veins during inspiration, is probably of little importance. It is supposed to be due to the existence of pericardial adhesions, which prevent the normal inspiratory dilatation of the right ventricle.

On palpation there is perceptible *enfeeblement*, or it may be, *disappearance of the impulse of the heart* in some cases of pericardial adhesion. It is not, however, distinctive of adhesion, as it may be present also in myocardial degeneration, in pericardial effusion, and when there are changes in the anterior border of the left lung. Owing to the adhesions, the position of the impulse of the heart does not, as a rule, alter with change of position of the patient or with respiration; when present this is a valuable sign.

Durozoiz has insisted on the necessity of considering together the sign of retraction as observed on inspection, and of the simultaneous shock of systole as observed on palpation as affording a diagnostic sign of much value.

Shock, synchronous with the heart's diastole, is perceived in occasional cases by the hand placed over the area of cardiac impulse. It is probably due to the rebound of the fibrous adhesions put on the stretch by the heart's contraction. By some observers it is regarded as pathognomonic.

The *pulsus paradoxus* is a sign of doubtful value. The pulse, if at all affected by respiration, normally becomes slightly fuller and stronger toward the end of expiration. The *pulsus paradoxus* grows weaker and smaller, and may even disappear in deep inspiration, regaining its usual volume at the close of expiration. It occurs in other conditions than adherent pericardium, so that it is not a sign of material diagnostic value. It "is of value in the diagnosis of indurative pericarditis only when there is a concomitant inspiratory engorgement of the jugular veins, a symptom which indicates a stenosis of the jugular veins during inspiration" (Sahli).

On *auscultation* the heart sounds will be found weakened, except during the period of decided cardiac hypertrophy, when they are distinctly accentuated. In mediastino-pericarditis, sometimes fine friction rales of a parchment-like character are audible along the margin of the lungs at their junction with the area of superficial cardiac dulness; if they persist during the cessa-

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tion of respiratory movements they furnish strong proof of the existence of pleuro-pericardial adhesions. A creaking sound over the body of the sternum is, in some cases, audible during up-and-down movements of the arms (Babcock). In some cases a bruit is heard resembling the harsh sound of a presystolic murmur (Hale White).

Wenckebach has drawn especial attention to the inspiratory difficulty often met within from adherent pericardium. The strong adhesions that form between the heart and root of the lungs on the one hand, and the wall of the chest and the central tendon of the diaphragm on the other, when the inflammation has been extensive (mediastino-pericarditis) so anchor the diaphragm that it cannot descend, carrying the heart with it in inspiration. The capacity of the chest is thus not increased in its vertical direction. The lower part of the chest is also bound down, so that the inspiratory capacity has to depend on the lifting upward and forward of the upper part of the chest, and the lateral expansion of the lower parts.

In the cases of "pericarditic pseudo-cirrhosis of the liver" and "multiple serositis," there is increasing dyspnœa and great ascites, and, later, dropsy of the lower extremities. There may also be effusion into the pleural cavities.

There may be a similar group of symptoms without chronic inflammation of the peritoneum; in these cases the pericarditic changes affect chiefly the portal circulation. In some cases there is genuine hepatic cirrhosis, the diagnosis from which is possible only when there is thorough appreciation of the symptom group, due attention being given not only to the history of the case but also to the cardiac signs of adhesion of the pericardium, such as systolic retraction, absence of apex impulse, immobility of the area of precordial dulness, and restriction of the expansion of the lower part of the chest in inspiration, especially on the left side.

Diagnosis.—In regard to diagnosis there are three classes of cases of adherent pericardium: (1) Those in which the signs and symptoms are so significant that a diagnosis can be made with ease and certainty; (2) those in which, after a careful investigation of all the symptoms and signs in the light of the history of the case, a probable or often only a possible diagnosis can be made; and (3) a large class of cases in which there is no history, nor either symptoms or signs to justify even a suspicion of the existence of adhesion of the pericardium. This third class includes practically all cases of simple adhesion of the pericardial surfaces without material exudate between them, and in which there has been no extrapericardial inflammation to cause adhesion to surrounding structures.

In the first class the signs are so typical, or there is such a conjunction of them, as to render diagnosis quite certain. Such a case was that of a lady, aged thirty-five years, who had been engaged in mission work in China for some years, and who wished advice as to her fitness to return to work. Five years previously she had a severe and protracted pericarditis from which she made a slow and incomplete recovery, palpitation and dyspnœa on exertion persisting and growing gradually more pronounced. On examination, well-marked systolic retraction was found to occur in the lower precordial region, affecting the fifth and sixth costal cartilages and lower end of the sternum, but showing itself chiefly in the intercostal spaces and the epigastric surfaces between the left costal margin and the ensiform cartilage. There was no respiratory movement of the epigastrium. The area of dulness extended from the right margin of the sternum to

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one-half inch outside of the left nipple line, and was not altered by respiration or change of position. Palpation showed a systolic shock synchronous with the recession, but no diastolic shock could be perceived. There was, in this case, the history of such an attack as would probably cause not only adhesion of the pericardium, but also infection of the myocardium on the one hand, and of the pleura and mediastinal tissues on the other; none of the essential signs of the condition of chronic fibrous mediastinopericarditis were wanting.

In the doubtful class of cases a diagnosis can frequently be made if the possibility of the existence of the affection is not overlooked, and due consideration given to the symptoms and physical signs. In many cases the symptoms are out of proportion to the signs and may be accounted for by the occurrence of adhesions. The symptoms are those of failing circulation and dilatation of the right ventricle without adequate cause to account for it. If suspicion is once aroused, evidence may be found to render a probable diagnosis justifiable. A protracted history of recurrent pericarditis is significant; and, if the patient has been under observation, the progress of inflammation may have been shown by the appearance of friction rubs at various points from time to time, together with an increase of the area of precordial dulness which remains undiminished after the pericarditis has been relieved. In such a condition effusion must be excluded, and due allowance must be made for dilatation of the heart.

Other physical signs may be found to guide to a correct conclusion, such as fixation of the apex beat and area of precordial dulness, systolic retraction of the lower posterior part of the chest, defective descent of the diaphragm and restricted expansion of the lower part of the chest in inspiration, weakness of the cardiac sounds and impulse as compared to the size and regularity of the heart, *pulsus paradoxus*, diastolic collapse of cervical veins, increasing swelling of the liver, etc.

In adherent pericarditis with secondary pseudo-cirrhosis of the liver and general serositis, the diagnosis is often difficult, especially in differentiating it from ordinary hepatic cirrhosis. In the latter affection there is usually a history of a cause such as alcoholism or syphilis, while in adherent pericarditis and multiple serositis there is often a history of rheumatism with, in some cases, pericarditis, or an acute illness in which precordial pain, distress, and other symptoms which may have been due to pericarditis were present. In ordinary cirrhosis there are often gastric or intestinal hemorrhages and the dropsy begins as ascites, œdema of the lower extremities following later; in the pericardial cases the œdema may precede the ascites if the changes in the liver and serous membranes are late in developing.

Great dilatation of the heart without hypertrophy, and not due to affection of the cardiac orifices, nor to lesions of the lungs, kidneys, arteries, stomach, etc., is probably caused by adherent pericardium (Potain). This is especially true in young persons; in advanced years, chronic change in the myocardium is more likely to be a cause.

It is on the consideration of the symptoms in general, rather than of any special ones, that the diagnosis can be made: systolic precordial retraction, the fixation of the diaphragm, the restricted inspiratory expansion of the lower part of the left chest, the loss of apical impulse, the diastolic shock, the rolling movement of the heart, the unchanging dulness, and the paradoxical pulse. Some of these may be present, and taken in association

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with the clinical history will usually render a positive diagnosis possible. As between rheumatic and tuberculous pericardial adhesion a differentiation may be possible. In the rheumatic cases there is always enlargement of the heart, a dyspnœa of long duration, and forcible precordial impulse with variable murmurs. In the tuberculous cases the heart is usually of normal size; there is little, if any, dyspnœa or palpitation; the impulse is feeble and the heart sounds weak.

Prognosis.—This depends on the nature and extent of the adhesions and the amount to which the heart substance has been implicated in the inflammatory process. If the adhesion consists merely of agglutination of the two pericardial layers, however intimately, it can scarcely cause any change in the condition of the heart or affect its functions, and is usually quite unsuspected until discovered at the autopsy. In more severe cases the myocardium is involved to a great degree in the inflammatory process. In most cases it is to the degenerative and fibroid changes resulting from the inflammation that the subsequent dilatation and failure of the heart are chiefly due. The action of the heart will be hampered by the new connective tissue and usually still more by the adhesions to surrounding structures, especially such as are unyielding as the chest wall and diaphragm.

Adhesions acquired in early life, especially those resulting from acute articular rheumatism, are usually followed early by serious functional disturbances; the younger the child the graver and more rapid the development of the symptoms. Rheumatic adhesive pericarditis has been regarded as the usual cause of cardiac failure in children. The gravity of the condition is greatly increased by the liability to recurrences of the pericardial inflammation, and by the co-existence of endocarditis or valvular affection. The occurrence of adhesive inflammation of other serous membranes—polyserositis—and extension of the inflammation to the mediastinum greatly increase the gravity of the prognosis. When the signs of cardiac failure, such as anasarca and ascites, develop, restoration of cardiac competency is difficult to establish and a fatal ending usually comes within a few weeks or, at most, months.

The disappearance of the systolic retraction is of grave omen as it indicates progressive enfeebling of the heart's energy. The failure of the heart to respond to digitalis indicates profound alteration of its muscular fiber, and adds to the gravity of the prognosis.

Death usually results from cardiac asystole, sometimes after the first, more often after a succession of crises; it may occur with symptoms of syncope or of an anginal attack.

Treatment.—The treatment is purely symptomatic. All rheumatic attacks in children, however slight, should be carefully treated, rest in bed from time to time being especially observed in order if possible to prevent affections of the heart or its membranes. As already remarked, the salicylates are generally regarded as having little influence on rheumatic cardiac affections, besides having a dangerously depressing effect if there is infection of the myocardium; given, however, at the onset of the rheumatic attack they probably shorten it and thus render a heart affection less liable to occur. Cold or hot applications, and, especially, small blisters to the precordium, often do much good. Digitalis in moderate doses, to stimulate a vigorous systole and so lessen the liability to adhesions, may do much good, and should be continued for long periods. Respiratory gymnastics, by stimulating the

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vigor of the heart's action, will also aid in lessening the tendency to adhesions.

Once the adhesion is established, the treatment has for its chief aim the development and preservation of the cardiac hypertrophy. To this end the heart should be guarded from overstrain. This calls for the intelligent cooperation of the patient, who should therefore be carefully instructed, without unduly alarming him, as to the dangers and how best to avoid them. Graduated systematic exercises recommended in valvular disease of the heart, judiciously used, should be of benefit in this condition. In both cases the object of the exercises is to develop the muscular power of the heart so as to maintain an efficient circulation.

The secondary effects from venous congestion of the digestive organs and the kidneys require frequent periodical recourse to active cathartics to reduce fulness of the portal system. For this purpose nothing serves the purpose better than a blue pill, or 1 or 2 grains (0.06 to 0.13 gm.) of calomel at night, followed next morning by Epsom salts or an aperient water. Such a course necessitates careful examination of the patient from time to time. Digitalis, or one of the other heart tonics, should be given if failure of the heart is threatening. When compensation yields and the venous side of the circulation becomes overloaded, complete rest is called for. The blood should be depleted by hydragogue purgatives, and if this is not successful, by venesection.

The diet should be nutritious and of small bulk so as not to overload the stomach. The quantity of liquids should not be excessive, in order not to unduly increase the volume of the serous fluid in the body and thus add to the labor of the heart.

Digitalis is often disappointing owing to the degeneration of the heart muscle. Caffeine, grains 2 to 5 (0.13 to 0.3 gm.); diuretin, grains 15 (1.0 gm.), and fluidextract of apocynum cannabinum, minims 2 to 10 (0.13 to 0.6 cc.) may prove useful. Strychnine may do good and is best given hypodermically. For pain and restlessness, morphine should be given; it is also the best tonic for an overstrained, irritable heart. Anasarca may require drainage, which should be done under strict asepsis.

In cases with marked systolic retraction of the costal cartilages and lower end of the sternum, operation to separate the adhesions more or less widely has been proposed by Delorme.[1] It must be an operation of doubtful value as well as doubtful safety. The adhesions would probably be formed again in a short time. Brauer[2] has carried out a much more effective operation for the relief of the condition. The operation, which he designates "cardiolysis," consists in resection of the ribs and cartilages, and even the margin of the sternum, to which the heart and tissues about the pericardium are adherent. The periosteum, as well as the ribs and cartilages, is removed. The object is to convert the resisting chest wall in the regio cordis into a soft, yielding tissue, so as to allow the heart to contract with ease and the diaphragm to descend in inspiration, carrying with it the heart and the roots of the lungs. By this means not only is the heart relieved of much that hampered its action, but, by allowing the diaphragm to descend, the respiratory capacity of the chest is greatly increased.

[1] *Traité de Méd.*, tome viii. p. 62.
[2] *Arch. f. Klin. Chir.*, Band lxxi, Heft 1.

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TUBERCULOUS PERICARDITIS.

Pericarditis in tuberculous subjects is not very rare, and may be due to a variety of infectious agents. This condition must not be confounded with *tuberculous pericarditis*, which is due to infection of the pericardium by the tubercle bacillus; this is relatively a rarer affection than pericarditis in the tuberculous. There is probably a fallacy in the opinion as to the frequency with which pericarditis in tuberculous subjects is regarded as non-tuberculous. It is generally accepted that many cases of simple pleurisy, with sterile exudate are due to tuberculous infection, and pericarditis with sterile exudate may likewise be as frequently due to the same cause. The exudate in many cases of pleurisy, which has been found sterile to microscopic and cultural methods of examination, has on inoculation into animals proved to be tuberculous. There is good reason to believe that this will be found equally true of pericardial effusions.

Etiology.—It is only during the last fifty years that tuberculous pericarditis has come to be generally recognized as a definite form of pericardial disease. The increasing attention attracted by tuberculosis has led to its being recognized with greater frequency.

It has been observed at all ages. Duckworth met with a case in a child of five months, and Lejard in a woman at the age of eighty-eight. It occurs probably most often in young adult life, and in males more frequently than in females.

In common with other parts, the pericardium is affected in miliary tuberculosis. Apart from this general infection, tuberculous pericarditis may occur as a primary and a secondary infection. The view is becoming more and more widely accepted, that the lymphatic glands are always the first seat of tuberculous infection, and that the various organs and tissues subsequently infected are invaded by way of their lymphatic vessels. If this theory is correct, and it probably is so, the terms primary and secondary largely lose their significance. Osler is, therefore, probably quite correct in regarding as primary all those cases "associated only with caseation of the bronchial, or, particularly, the anterior mediastinal glands," as these glands are probably in all cases affected before the pericardium is invaded.

Most cases of tuberculous pericarditis develop secondarily to infection of other organs, such as the lung, pleura, sternum, vertebræ, peritoneum, or even the intestines. The reason for the rare, and usually late, invasion of the pericardium probably lies in its relatively scant vascular supply. In rare cases there has been penetration of the pericardium by a neighboring tuberculous gland resulting in direct infection of the pericardial cavity.

Special Pathology.—In tuberculous pericarditis are found many of the lesions common to other forms of pericarditis, as well as some of the distinctive lesions of tuberculosis.

The pericarditis may be of the *dry* form, or be accompanied by *effusion*. In the dry form the condition terminates nearly always in adhesion of the pericardial surfaces; in the form with effusion, adhesion may also occur after absorption of the exudate has taken place.

The effusion may be serous, serosanguinolent, or frankly hemorrhagic, but is rarely purulent. The occurrence of even a small quantity of blood

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in the serum is of real diagnostic value. The quantity of effusion is variable; it may not be more than demonstrable at the autopsy, or may be very abundant. Hudels reports a case in which there were 2 liters, and in a boy aged twelve, a patient of the writer's, 1⅓ liters (45 ounces) of serosanguinolent fluid were removed at the third aspiration.

In many cases, tubercles are not demonstrable postmortem; if present, they are often very small. They occur most frequently on the parietal layer along the course of the small bloodvessels, the infection having been conveyed by lymphatics to the pericardium from diseased structures in the mediastinum. They are found most frequently beneath fibrinous exudate in the meshes of the new fibrous-tissue formation. Sometimes larger tuberculous masses are formed by aggregation of smaller deposits. Their external parts are grayish, while the interior consists of yellowish caseating masses. The deposits occur most frequently about the base of the heart. They may invade the myocardium and even penetrate its wall into the cavity of the heart, especially that of the auricle.

In the majority of cases there is a fibrinous exudate of variable degrees of thickness, deposited chiefly on the parietal pericardium. There may be excessive formation of new fibrinous tissue, at first grayish and translucent, but later becoming white and firm, as it is converted into dense cicatricial tissue which intimately unites the pericardial surfaces. If the exudate is purulent it may become inspissated, and this may, in time, become converted into a calcareous mass.

Symptoms.—As a rule, the affection is quite latent throughout its whole course, and is only discovered at the postmortem examination. This is accounted for, in the first place, by the fact that the disease of the pericardium usually begins insidiously and runs a subacute or chronic course, and, in the second place, that the pericardial symptoms are generally overshadowed by the symptoms of lesions in other organs.

In acute cases there is usually a rapid effusion, and the symptoms are similar to those of acute non-tuberculous pericarditis: pain, palpitation, some fever, friction sounds, dyspnœa, and the signs of effusion. The acute cases are generally due to infection from an adjacent tuberculous gland; and if the gland is caseous, the effusion may become purulent and obscure the tuberculous nature of the disease. The following case affords a good illustration of acute tuberculous pericarditis: A boy, aged eleven years, under the care of Dr. Harley Smith, had been ailing somewhat for a few weeks, and for a week or two complained of shortness of breath and some precordial pain. When Dr. Smith saw him, the temperature was 102° F. (38.8 C.), respirations 36, and pulse 120. There was some precordial fulness, and pericardial effusion was easily recognized. During the next five days the distress increased, the pulse became irregular and intermittent, and the signs of distention of the pericardium became more marked. A few days later, when the writer saw the patient with Dr. Smith, he was on a sofa lying in a half-recumbent position, turned somewhat to the right side. His expression was distressed and there was some cyanosis; the breathing was over 50 to the minute and labored. The temperature was normal; the pulse was small, weak, and about 150 to the minute. The precordium was very full, and flat on percussion from one inch to the right of the sternum to one inch outside the mammillary line on the left. No cardiac impulse could be felt and the sounds were not audible. The dia-

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phragm was depressed so that the flatness and board-like resistance of the precordium on percussion extended downward into the angle between the ensiform cartilage and the costal margin. These signs indicated that the heart lay upward and backward from the chest wall. The lower border of the liver was a finger's breadth below the costal margin.

His distress was so great that it was deemed advisable to remove the fluid without delay. The trocar was introduced at the highest part of the costal xiphoid angle on the left side. The point was directed backward until it penetrated to the posterior surface of the costal cartilage, and then it was turned upward and to the left, when it immediately entered the pericardial cavity. As soon as the trocar entered there was a free flow of blood-stained serous fluid. The precordial bulging soon began to lessen, the area of dulness diminished, the respiration became quieter, and the countenance less distressed. Eighteen ounces (520 cc.) were withdrawn, and the cannula, then coming into contact with the heart, was removed. The cardiac impulse was now visible, and the sounds audible, although weak. The liver receded beneath the costal margin. The pulse became regular, fell to 120 per minute, and improved in volume. He was now able to lie down in comparative comfort, and he rested well the following night.

During the following six days the signs of pericardial effusion gradually increased, and the area of dulness extended farther in all directions than at the time of aspiration. The temperature varied from 99° to 104° F. On April 8 the liver was two fingers' breadth below the costal margin, and there was much respiratory distress. The pulse was rapid and irregular, being especially weak and often lost in inspiration, the *pulsus paradoxus*. Aspiration was repeated, the trocar being introduced in the fifth left intercostal space one inch from the sternum, and 35 ounces (1050 cc.) of reddish fluid were obtained. The specific gravity was 1010; it was sterile to ordinary cultural methods. The pulse improved and the respiration became easier, but was still rapid and labored.

Next day, April 9, he was more comfortable, but the temperature began to rise and the pulse was rapid and weak. The fluid re-accumulated rapidly and by the 13th the distress was greater than on either of the previous occasions. The pericardial cavity was opened at the fifth interspace to the left of the sternum and a drainage tube was inserted. Forty-two ounces (1250 cc.) of blood-stained serum were evacuated. The surface of the pericardium within reach felt smooth. During the next day the discharge was free but lessened later, practically ceasing on the 15th. The left side became a little fuller than the right and the resonance over the lower lobe of the left lung became defective. At the back the dulness extended to the angle of the scapula, and over this area respiratory sounds were tubular. The general condition grew gradually worse, breathing became Cheyne-Stokes in character, and swallowing caused pain as the food passed through the lower part of the œsophagus. By the 23d the discharge, although scant, became seropurulent and offensive. Death took place on the 24th.

At autopsy (J. J. MacKenzie), upon opening the thoracic cavity, the most marked feature was the evident thickness of the parietal pericardium and the extension of the inflammation into the anterior mediastinum. There were some pleuritic adhesions upon both sides, but not extensive. Upon removing the lungs the visceral pleura and both lungs were found studded with miliary

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tubercles, and there was extensive old tuberculous disease of the anterior mediastinal glands, and of the glands at the roots of the lungs. The parietal and visceral pericardium was found to be, in some places, as much as one-half inch in thickness, due to the development of an extensive layer of granulation tissue (Fig. 1). A careful examination of the pericardium, especially in section, showed scattered tubercles. Both the lungs, liver, spleen, and kidneys were studded with miliary tubercles, which were quite small, and showed very slight evidences of caseation, so that the infection of these organs was

FIG. 1

Tuberculous pericarditis.

evidently quite a recent one. Much more advanced tuberculous disease was seen in certain of the mediastinal glands, especially in one which was in contact with the pericardium and was extensively caseated.

There seems no doubt that the history of the case is that which is so common in cases of tuberculous pericarditis, viz., an extension to the pericardium from tuberculous lymphatic glands at the root of the lung and in the anterior mediastinum. The pulmonary tissue showed no old focus, and the miliary condition was clearly secondary to the tuberculous disease of the mediastinal glands and the pericardium. It is quite possible that there may have been

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an extension of the infection through the wall of the right auricle where the heart wall is thinnest, causing the general systemic infection by way of the blood stream.

In most cases there are some of the general symptoms of tuberculosis, as loss of weight, anæmia, and weakness; if the tuberculous infection be more acute, there may be irregular fluctuations of temperature and profuse perspirations.

Tuberculous pericarditis is usually subacute or chronic, develops insidiously, runs a latent course, and is often so obscured by tuberculous disease of the pleura and lungs, that, in the majority of cases, the pericarditis is unsuspected until the autopsy shows its existence. This is doubtless often due to the possibility of the occurrence of the disease being attended by no marked symptoms, and its existence therefore not sought for. If systematic careful examination is made, whether as a matter of routine or because of functional disturbances of the heart, there will be found in tuberculous pericarditis the signs which have already been described as indicating the simple acute disease, whether dry, with effusion or with adhesions, but there will be nothing in the signs to indicate its tuberculous nature.

In the majority of cases, however, the course is chronic, and other manifestations of tuberculosis, especially of the pleura, usually suffice to reveal the nature of the pericarditis. Large effusion is exceptional, but if it is so great as to necessitate aspiration, and the fluid proves to be hemorrhagic, it affords strong evidence of the tuberculous nature of the affection.

The two layers of the pericardium become thickened and adherent if there is no effusion, and may contain tubercles or caseous masses between the layers. The symptoms and signs will be those of adherent pericardium.

Diagnosis.—Neither the symptoms nor the course of the pericarditis are sufficient to enable us to affirm the tuberculous nature of the affection. The signs of tuberculous disease in other organs and structures, especially of the serous membranes, makes the existence of a similar infection of the pericardium very probable. Hemorrhagic fluid obtained on aspiration is also strongly presumptive evidence, but even with all these conditions the pericarditis may still be due to a rheumatic or other cause. Examination of the fluid may show tubercle bacilli, but their absence from the effusion does not prove the fluid to be of non-tuberculous origin, as the exudate in serous effusions is often sterile, but the inoculation into animals frequently gives positive results.

Prognosis.—If the symptoms are so marked that the condition is readily recognized the outlook is not good, most cases terminating fatally early, directly from the pericardial affection, from co-existing disease in other organs, or from general tuberculosis. In some of the many cases in which the diagnosis is made postmortem, it is impossible to be certain of the duration of the pericardial disease, which may have had little or nothing to do in causing death.

In the absence of serious affection of other organs, tuberculous pericarditis usually runs a chronic course. A sharp onset followed by an acute course is exceptional. The occurrence of pericarditis in arrested or quiescent tuberculosis greatly increases the liability to renewed activity in the other lesions. Death is usually due to the general tuberculous disease or to cardiac failure. Profuse intrapericardial hemorrhage and pulmonary thrombosis have caused death in a few cases.

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If adhesions of the pericardial surfaces take place, a cure results so far as the pericarditis is concerned, but cardiac failure is probably not distant, being especially liable to occur in the tuberculous. The occurrence of tuberculous pericardial effusion in a tuberculous subject generally hastens the fatal ending.

Treatment.—The treatment of tuberculous cases is to be carried out as in other forms of pericarditis. If the fluid is abundant, it must be removed; after a time it usually re-accumulates. Caution is necessary lest the lowering of intrapericardial pressure cause rupture of fresh vessels and further hemorrhage. In a recent case, after two aspirations required at short intervals on account of the rapidity of the effusion, an injection of naphthol camphor into the pericardial cavity was followed by an early cure.[1]

The general treatment is to be directed to the condition as indicated in each patient.

HYDROPERICARDIUM.

Hydropericardium, or *hydrops pericardii*, signifies a serous non-inflammatory transudation into the cavity of the pericardium, similar to that occurring in hydrothorax or ascites.

The quantity of serum normally in the pericardium is somewhat indefinite, but there is probably not usually more than sufficient to moisten it, although the quantity is doubtless subject to variation. At autopsy there are usually found 5 to 10 cc. or even up to the 100 cc. of clear, straw-colored, alkaline fluid, containing various salts, urea, and sometimes traces of sugar. It is said to contain more fibrin than any of the other serous transudations. Much of the transudate probably escapes at the time of death, and possibly for a time afterward.

Although the condition is analogous to pleural and peritoneal dropsical effusions, it does not occur with nearly such great frequency. It, however, probably exists, in at least a moderate degree, in all cases of marked hydrothorax.

Etiology.—The causes of hydropericardium are either local and of a mechanical nature, or general from blood changes in cachectic states and nephritis.

Among the former are such as impede by pressure the pericardial circulation, and thus cause venous stasis, from which results the serous transudation; among them are lesions of the heart and lungs which obstruct the general venous circulation, including that of the heart and pericardium; local affections, such as neoplasms and cicatrices in the heart, pericardium, or mediastinum, which obstruct the veins and capillaries of the pericardium, and cause transudation on account of the local stasis.

Carcinoma and tubercle of the heart and pericardium are the causes in some cases, the latter being most frequent; in such cases the effusion occurs without there being demonstrable venous obstruction, as is the case also in peritoneal dropsy. The accumulation of the fluid is probably due to occlusion of the lymphatic openings by antecedent swelling of the pericardial epithelium. Sclerosis of the coronary arteries and thrombosis of the cardiac veins have been assigned as causes.

Among the general causes are, the cachexias of nephritis, tuberculosis,

[1] Rendu, quoted in *Traité de Médecine*, tome viii, 69.

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carcinoma, malaria, leukæmia, etc. In these cases the pericardial dropsy is usually associated with dropsy of other serous cavities.

Symptoms.—Hydropericardium usually develops gradually without special symptoms; its occurrence is, as a rule, overshadowed by the symptoms of the cause on which the effusion depends, and by the hydrothorax with which it is nearly always associated. When the collection of fluid becomes considerable, its presence is shown by the physical signs of pericardial effusion; enfeeblement of the impulse and sounds of the heart, increase of the area of precordial dulness, and, it may be, fulness of the precordium. There is no friction rub. If there are no pericardial adhesions, the area of flatness on percussion is decidely modified by respiratory movements and changes of position of the patient, especially on his assuming a stooping position. In cases of marked emphysema, the area of dulness is difficult to determine, and is little affected by position. There is no fever or pain in hydropericardium. Yet in cases of rapid effusion there may be some precordial distress and a feeling of thoracic constriction with dyspnœa, and disturbance of the action of the heart as in pericarditis; in these cases, some affection of the substance of the heart is probable, but in the absence of involvement of the heart these symptoms are at least less severe, although they are marked in proportion to the rapidity of the effusion. The effusion is usually a terminal occurrence, and takes place so slowly and unobtrusively that it is rarely recognized unless sought for.

Diagnosis.—A diagnosis is to be made on the basis of the signs of effusion into the pericardium without the phenomena of pericarditis, and the co-existence of fluid accumulation in the other serous cavities, of general dropsy, and of venous stasis. A consideration of the etiology is important. Often however, it is difficult to differentiate hydropericardium and chronic pericarditis without febrile reaction occurring in nephritis or tuberculosis. The error is not of material importance in its practical application.

Prognosis.—The gravity of hydropericardium is usually to be measured by that of the affection on which it depends; this affection often causes an early fatal termination. The debility in the case may be so marked that the effusion, by its abundance, may itself endanger life. The effusion does not diminish or disappear unless the condition on which it depends is relieved or cured.

Treatment.—The treatment is directed to the primary disease to which the hydropericardium is due—tuberculosis, chronic malaria, nephritis, or the state of cachexia.

An effort may be made to lessen the tendency to exudation by diuretics, hydragogue purgatives, and diaphoretics, but these measures are rarely successful. The calcium salts, as the chloride and lactate, may lessen the exudation by increasing the coagulability of the blood. When the exudate is large, relief of the symptoms may be obtained by aspiration, but it is, as a rule, only temporary, as re-accumulation is usually rapid. Aspiration is, however, rarely called for, as the patient generally suffers chiefly from the primary affection, and only in a slight degree from the hydropericardium.

HÆMOPERICARDIUM.

By this is meant an effusion of blood into the cavity of the pericardium. This condition does not include the forms of pericarditis in which there is

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more or less blood in the effusion. A hemorrhagic pericarditis may occur in grave fevers, in scorbutus, cancer, tuberculosis, alcoholism, and in old age. In serofibrinous effusions there may be more or less coloring of the effusion by the blood escaping from ruptured vessels in the new membrane, or from the solution of hæmatin. Neither does the term include cases of ecchymoses of the pericardium due to grave intoxications, as phosphorus poisoning especially, or to the acute venous stasis caused by suffocation and strangulation.

Etiology.—The causes of hæmopericardium may be medical or surgical. Of the surgical causes, the most frequent are such traumatic injuries as penetrating and gunshot wounds; rupture of the pericardium by crushing injuries, falls from high places, or by penetration of fractured sternum or ribs; and traumatic rupture of the heart.

Among the medical causes the most frequent is spontaneous *rupture of the heart*, as a rule during violent strain; it is usually the result of degeneration of the wall of the heart, especially if a cardiac aneurism has existed. In some cases rupture of an aneurism of the coronary arteries is the source of bleeding. Rupture of an aortic aneurism into the pericardial cavity is not rare. In some cases an aneurism situated above the pericardial covering of the aorta dissects the coats down to the attachment of the aorta to the heart, and then ruptures into the cavity of the pericardium; the rupture may be small, so that the bleeding takes place slowly.

Special Pathology.—The quantity of blood in the pericardium varies in different cases; it depends chiefly on the size of the rupture and, consequently, on the rapidity of the bleeding. The more rapid the escape of the blood the less will be the quantity, as the result is quickly fatal; the quantity of blood may not exceed six or eight ounces. On the other hand, if the hemorrhage is slow the patient survives a relatively long time, and the volume of blood that has escaped may greatly distend the pericardium. Rolleston describes a case with a pinhole opening in the external coat of the aorta in which there were twenty-four ounces in the pericardium, and Mansell Moulin, one, with recovery, in which six pints were removed in the course of several hours.

The blood may be fluid, or coagulated wholly or only in part. In a case of Whittaker's[1] several layers of coagulated blood were stripped from the pericardium, the blood having escaped through a rupture in the heart, and in small quantities at a time, in the several days during which the patient survived after the accident. In nearly all cases the source of the bleeding is easily demonstrated.

Symptoms.—There is much variation in the intensity of the symptoms. If the effusion of blood is rapid, death is sudden, or at least not long delayed, and due to compression of the heart, syncope, or sudden, cerebral anæmia.

If the escape of blood is slow, there are the physical signs of pericardial effusion with the general symptoms of internal hemorrhage, such as pallor, vertigo, tinnitus aurium, small pulse, syncopal attacks, and occasionally convulsions. The onset may be with a sharp pain, or a feeling of something having given way. Death always follows within a short time.

Diagnosis.—The diagnosis is usually difficult, and often only correctly made *postmortem*. Following injuries, it may be evident from the nature of

[1] *Twentieth Century Practice of Medicine*, vol. iv, p. 50.

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the cause. The diagnosis may be made if there are the signs of sudden pericardial effusion and of internal hemorrhage.

Prognosis.—The prognosis is always grave, and usually hopeless, death occurring at latest within a few days. In traumatic cases with moderate hemorrhage and an injury not necessarily fatal, recovery may take place, but cases due to rupture of the heart or of an aneurism, are almost necessarily fatal, although life may be prolonged several days. Travers reports a case of extensive traumatic rupture of the right ventricle in which death did not occur until the eleventh day.[1]

Treatment.—The treatment in rapidly fatal cases is wholly ineffective. Ordinarily it should be directed to the cause and to counteracting the effects of the loss of blood. Operation, with the object of suturing the rupture of the heart, may be successful in some traumatic cases, and should be tried in suitable ones.

PNEUMOPERICARDIUM.

Pneumopericardium consists essentially of a collection of gas in the cavity of the pericardium. In nearly all cases there is at the same time an effusion of serum (hydropneumopericardium); of pus (pyopneumopericardium); or of blood (hæmopneumopericardium).

The condition was recognized by the older authors, and it was very fully described by the writers of the middle of the last century. The descriptions were very much more full than those found in even the large works of the present day. The signs and symptoms are so characteristic, and they not only described but interpreted them correctly, that there is no doubt of the correctness of their diagnosis.

The affection is of very rare occurrence. James,[2] in 1904, was able to find only 37 undoubted cases in the literature; he added 1 of his own, making a total of 38 cases. To his valuable review of the literature, the writer is much indebted.

Etiology.—Three groups of causes may give rise to the presence of gas in the pericardium; putrid decomposition of an exudate, the entrance of air through a traumatic opening, and perforation of the pericardium by an ulcerative process in a neighboring air-containing organ.

The first group presupposes the possibility of the production of gas by putrid decomposition in a closed sac. Cases with autopsy have been reported by several observers, such as Stokes, Friedreich, Duchek, Bricheteau, and others. They presented no peculiarity further than the presence of gas and purulent collections in the pericardial cavity. It is evidently an extremely rare form, if it exists at all. But its occurrence in an advanced state of *postmortem* decomposition is not a rare event; this may account for some of the cases reported. In James' 38 collected cases there were 5 cases without perforation in the pericardium. In 1, Stokes' case, there was acute pericarditis with recovery; in the 4 fatal cases no opening was found at the autopsy.

In the second group there is a perforating wound into the pericardium by a sharp instrument or foreign body, by a gunshot wound, or by a trocar

[1] *Lancet*, September, 1906, p. 706.
[2] W. B. James, Pneumopericardium, *American Medicine*, July 2, 1904, p. 23.

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in the operation of paracentesis; in such cases the presence of the gas is due to the entrance of air either directly, or from the pleura in pneumothorax by the rupture of adhesions, or from puncture by a foreign body in the œsophagus. Perforation may be caused by a fractured rib, or a crushing injury may lacerate the lung, pleura, and pericardium, and permit air to enter from the torn lung. These were the causes in 18 of James' collection.

In the third group the ulceration may be either in a hollow air-containing organ contiguous to the pericardium, or in some structure the seat of a purulent inflammation; in either case the ulceration may lead to an opening between the pericardium and a hollow viscus, and permit the entrance of air into the former. The most frequent processes that occasion such an accident are: an ulcerating cavity in the lung, pyopneumothorax, cancer of the œsophagus, gastric ulcer perforating the diaphragm, and a subdiaphragmatic abscess perforating both pericardium and stomach, or, possibly, the intestine. There were 15 cases due to these causes in James' collection.

Owing to the entrance of microörganisms, pericarditis is very frequently associated with pneumopericardium, and as the germs are usually pyogenic the inflammation is nearly always purulent. Mueller is said to have met with a case of serous exudate, and Stokes reports a case of acute pericarditis followed by hydropneumopericardium with cure.

In 7 cases, air entered from the œsophagus; in 3 of these from perforating cancerous ulceration, 1 from unspecified ulceration, and in the remaining 3 from traumatism. In 8 cases air entered through a penetrating wound from without; in 4 from a softened tuberculous focus in the lung or in a lymph gland; in 7 from crushing injury causing fracture of the ribs or sternum, and laceration of the pericardium; in 2 from an abdominal abscess, 1 of the liver, and 1 of the appendix. In 2 it was from gastric ulcer; in 1 from pneumothorax; in 1 from pneumonia with gangrene of the lung, perforating the pleura and later the pericardium. In 1 case, some disease of the lung perforated into the œsophagus and later into the pericardium.

Special Pathology.—The essential condition consists in an accumulation of gas in the upper part of the pericardial cavity, a collection of liquid in the lower part, and the existence of a pericarditis, usually intense, either primary, or secondary to a rupture of the serous membrane.

The composition of the gas is very variable; it is usually of fœtid odor, and there is putrid decomposition of the purulent exudate. The pericardium is usually distended, and on puncture the gas escapes with a hissing sound.

The displacement of the neighboring organs, as the lungs, diaphragm, etc., and the displacement of the heart, presents nothing of unusual character. In some cases, the opening in the pericardium had become closed.

Symptoms.—The symptoms vary greatly according to the cause of the condition and the nature of its onset. If the condition develops gradually, the symptoms will be those of a mild pericarditis until the distention of the sac becomes great, and causes symptoms of pressure on neighboring organs and functional disturbances of the heart. But in the traumatic forms, the entrance of air is sudden and marked by the brusque appearance of subjective phenomena, such as sudden retrosternal pain of a burning, hot character, precordial oppression, palpitation, dyspnœa, and of thready pulse, cyanosis, etc. There may be recurrent syncopal attacks. The symptoms closely resemble those presented by the various forms of pneumothorax. Dysphagia from pressure on the œsophagus has been reported (Eisenlohr).

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The *physical signs* are, in most cases, strikingly characteristic. This is shown by the frequency with which the cases were recognized by all observers, nearly all of whom were meeting with the condition for the first time. In only 6 of the 38 cases was the condition not recognized before autopsy (James). On inspection, the precordial region is usually seen to be prominent, at least in the intercostal spaces, and the cardiac impulse is not visible. On palpation the cardiac impulse is feeble or absent, but may return with normal force and become visible if the patient assumes the prone position. The percussion sound is tympanitic, of a metallic character, and disappears as the patient assumes the prone position.

As the effusion increases, the lower part of the precordial area becomes flat, the upper remaining tympanitic; with change of position of the patient there is a corresponding change in the relationship of the areas of tympany and flatness, the former being always at the upper, and the latter at the lower part. Systole may bring the heart against the chest wall and the note will then be dull. Cracked-pot sounds may be present even without a communication between the pericardium and a bronchus (Stokes).

Auscultation affords the most characteristic sign of the presence of fluid and gas, in the churning, splashing sounds audible over the precordium and synchronous with the heart's action, whether regular or irregular. It was noted in one-half of James' collection, under a variety of descriptions, as bruit de Moulin, de roue hydraulique, metallic gurgle, etc. It is of the same character as the succussion sound produced by shaking a patient with hydropneumothorax. Metallic tinkling sounds were heard in 24 cases, also synchronous with the movements of the heart, and usually blended with the churning, splashing sound. The tinkling may be audible at a distance from the patient, who may himself hear it, and be conscious of the tumultuous action in his chest. As the liquid exudate becomes abundant the cardiac sounds are weakened and may disappear; more often they are masked by the various pathological sounds.

Pericardial friction sounds of variable intensity are frequently heard, and, in some cases there is a fine crepitation due to emphysema of the cellular tissue situated in front of the pericardium.

Diagnosis.—This is usually easy on account of the marked and characteristic signs. The condition might be simulated by left pneumothorax, especially if confined to the outer part of the pleura, and by a large pulmonary cavity in contact with the pericardium. In such conditions the normal outline of the heart, its impulse, and the arrest of the various churning, metallic, and other sounds on suspending respiration would give a correct diagnosis.

Gaseous distention of the stomach sometimes causes metallic heart sounds, but confusion with pneumopericardium should not occur if the existence of the normal area of heart dulness, the cardiac impulse, and the absence of material functional troubles and disturbances of the heart are taken into consideration. The passage of a stomach tube would give vent to the gas and definitely settle the diagnosis.

Emphysema of the tissue in front of the pericardium from traumatism presents some of the signs of pneumopericardium.

Prognosis.—Of the 38 cases collected by James, 26 terminated fatally, and 11 in recovery. In 8 of the 26 cases nearly all the causes of the pneumopericardium were in themselves fatal; they were such as cancerous and other

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perforations of the œsophagus, gastric ulcer and hepatic abscess perforating the diaphragm, and tuberculous ulceration and gangrene of the lung opening into the pleura and later into the pericardium.

The large number of recoveries shows that the heart is remarkably tolerant of pericardial disease, that is, so long as its own substance is not involved. Much may depend on the suddenness of the distention of the pericardium with gas, as shock will be induced in the cases of sudden development, and add greatly to the danger.

Treatment.—In traumatic cases, the opening should be closed at once by an antiseptic dressing; this is the most important part of the treatment. Then every effort possible should be made to prevent purulent inflammation of the pericardium.

If an abundant exudate occurs, with the signs of a distended pericardium, and threatening cardiac collapse from compression, evacuation of the pericardial contents becomes necessary. The method by which the evacuation should be accomplished will be indicated by the character of the gas and liquid present. If the exudate is purulent and putrid, the original opening should be enlarged to give free discharge to the pericardial contents. Some advise irrigation with warm antiseptic solution; but if drainage is free this should not be necessary and, in any case, it can scarcely accomplish a good purpose. In fistulous cases the treatment is simply palliative, according to the requirements of each case.

NEOPLASMS OF THE PERICARDIUM.

The various neoplasms of the pericardium are malignant, as *carcinoma* and *sarcoma*, and non-malignant as fibroma, enchondroma, free bodies, and hydatids.

Malignant Neoplasms.—Cancer and sarcoma may be *primary* or *secondary*.

Primary cancer is very rare, even its occurrence is disputed. Of the cases reported it is not clear how many are cancer and how many are sarcoma. Sir W. Broadbent[1] reported a case of sarcoma of the pericardium in 1882, and Williams and Miller[2] a case of primary sarcoma in a girl, aged thirteen years. Broadbent's case was in a stout, florid man, aged twenty-three years, who complained of some discomfort in the lower part of the thorax, thought to be due to a disordered liver. He was ordered change and exercise. For two months he had had pain in the shoulders and down the arms, with dyspnœa on exertion. After the onset of the dyspnœa there were signs of fluid in the left pleura, also in the pericardium. He was unable to lie on the right side. Three weeks later there was no fluid in the pleura, but the pericardium was apparently distended and the dyspnœa was increased. He was tapped in the fifth interspace, half-way between the sternum and the nipple line, but no fluid was obtained; the trocar impinged upon a firm mass, which was not the heart, as it communicated no movement to the trocar. He was none the worse on account of the tapping, but died three days later. At the autopsy, the pericardium was found one-half inch thick at the base, the thickness

[1] *Transactions of the Pathological Society of London*, vol. xxxiii, p. 78.
[2] *New York Medical Journal*, April 14, 1900.

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increasing upward being one and one-half inches at the great vessels. On examination it proved to be sarcomatous.

Secondary growths are scarcely more frequent. In 477 cases of cancer in various parts, in only 7 was the pericardium affected (Williglk). Kobler met with cancer 6 times in 9118 autopsies. It may be secondary to cancer of the heart or of some neighboring part, as the mediastinum, the bronchial glands, the pleura, lung, or œsophagus. It is sometimes involved in cases of generalized metastatic nodules secondary to cancer of distant organs. In it are reproduced the anatomical characters of the original disease; this is true of sarcomatous growths also. They always give rise to pericarditis with more or less effusion, which may be serous, oftener hemorrhagic, and sometimes purulent or even putrid. In some cases the invasion occurs as a diffuse infiltration affecting more or less extensively the serous membranes and subjacent tissues; in others, the disease occurs in the form of distinct growths varying in size and number.

Symptoms.—The symptoms are those of mild or chronic pericarditis with the general, grave condition usually occurring in malignant affections. The subclavicular glands may be involved and render the diagnosis quite clear. If aspiration is rendered necessary by the abundance of the effusion, a hemorrhagic fluid is usually obtained; it is, however, occasionally purulent and even putrid. There may be the signs of primary or secondary carcinoma.

Diagnosis.—The diagnosis is easy if malignant disease can be demonstrated in other parts of the body. In the absence of such growths the diagnosis may be impossible. The possibility of a mediastinal tumor being malignant should be borne in mind; it may simulate pericardial effusion.

Prognosis.—The prognosis is necessarily fatal, and the duration brief.

Treatment.—The treatment is wholly symptomatic, the objects being to relieve distress and maintain strength. If the effusion is abundant, aspiration will be necessary; it is questionable if free drainage will be desirable, even if the exudate is purulent or even putrid.

Various Neoplasms.—Occasional reference occurs in the literature to non-malignant neoplasms in the pericardium. Bouchard reported a case of polypus in a child aged four years. Free bodies in the cavity of the pericardium have been found; they owe their origin probably to polypi or free fringes. They may consist of soft tissue, or of firm, fibroid structure, and are occasionally calcareous (cardioliths).

Fibroid tumors and *lymphomas* of the pericardium have been reported, and one case of cystic enchondroma has been met with.

Bouchard has described fringes resembling those met with at times in the knee and other joints; they are of occasional occurrence. They may be pedunculated, or even become free, forming soft, foreign masses. Foreign bodies may also arise from a coagulum of fibrin, or from inspissated pus in which lime salts have become deposited.

Hydatids.—Hydatids of the pericardium are very rare. The late Davies Thomas, of Australia, found the record of only two cases. Cases have been reported by Barlow, Enos and Rapp, Chadzynski, Bernheim, and MacDonald. In Chadzynski's case the cyst was very large and ruptured into the pericardial cavity. Hydatid cysts of the pericardium present no symptoms of special significance. As a rule, hydatids co-exist elsewhere and may guide to a correct diagnosis. In many cases, their existence in the pericardium is unsuspected until revealed at the autopsy.

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SYPHILIS OF THE PERICARDIUM.

The *pericardium* is so rarely the seat of syphilitic infection, and the few cases in which infection occurs shows such indefinite, if any, symptoms, that the subject is one of academic interest rather than one of practical medicine. Ricord, in 1851, was the first to describe the disease; in his case there was some fibrinous exudate on the pericardium. Virchow, in 1861, described the second case recorded; in this case there was adhesion of the pericardium. In 1897, Phillips[1] collected 25 cases of syphilis of the heart, and in 5 of these the pericardium was involved. Most works on diseases of the heart make no reference to the disease, and, of those that do, few give it more than a passing notice. Gibson[2] gives a fairly full description, and Babcock[3] discusses the subject at even greater length.

Etiology.—There is nothing known as to the causes that determine the infection of the pericardium. There is no apparent reason why it should escape more than other tissues, except its scant vascular tissue. Infection probably occurs only in the later periods of the disease, although doubtless it is possible that the pericardium, like any other structure, may become infected very soon after the appearance of the initial sore.

Special Pathology.—An adequate explanation for the relative immunity of the pericardium to syphilitic infection may be found in its slight vascularity. The point of syphilitic infection, in all organs and tissues, appears to be the wall of the bloodvessels, probably by way of the lymphatics. In proportion to its vascular supply, syphilitic disease probably affects the pericardium quite as frequently as it does the meninges of the brain. In nearly all the cases published the pericardial lesion has occurred in association with syphilitic disease of the subjacent muscular tissue. As a rule, only the visceral pericardium is affected and the lesion is usually a circumscribed inflammation, rarely a gummatous deposit. Beneath the inflammatory areas is usually found some fibrosis of the muscular tissue or a gumma embedded in the wall of the heart. The parietal pericardium in contact with the affected visceral layer may become infected; in that case a chronic thickening occurs in it from cellular infiltration. The vessels of the affected pericardium are hyperæmic, but as the new cicatricial tissue is organized and contracts, they become obliterated and a white scar results. There may be no fibrinous exudate formed on the surface of the pericardium; in that case no pericardial adhesions are found.

Fluid exudate appears to be rare, so that its presence, whether serofibrinous or hemorrhagic, is indicative of tuberculous rather than syphilitic disease.

Gumma of the pericardium is very rare. Marcek[4] was able to find only three undoubted cases described; since then no fresh cases seem to have been reported.

Symptoms.—Of the pericardial lesion itself there are probably no symptoms; the disease of the myocardium, with which it always appears to be associated, can, no doubt, cause all the symptoms that may be present during the course of the pericardial affection.

[1] *Lancet*, 1897, vol. i, p. 223.
[2] *Diseases of the Heart and Aorta*, 1898, p. 381.
[3] *Diseases of the Heart and Arterial System*, 1903, p. 138.
[4] *Archives f. Dermatologie u. Syphilographie*, Band xxv, S. 279.

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Diagnosis.—A pericardial lesion may be suspected in a syphilitic case that shows signs of a cardiac affection, but its existence can neither be demonstrated nor excluded. In rare cases, possibly, there may be a friction rub.

Prognosis.—Syphilis of the pericardium, of itself, can scarcely have any influence on the duration of life, and probably rarely causes any disturbances of comfort.

Treatment.—In so far as the pericardial lesion is concerned, the question of treatment is one of academic interest. In a suspected case, mercury and the iodides should be employed freely.

ABSENCE OR DEFECT OF THE PERICARDIUM.

Complete absence of the pericardium is rare; it is usual in cases of serious anomaly, such as ectocardia, etc. Partial defect is more frequent, the pericardium usually taking the form of a falciform fold projecting upward from the diaphragm and forming an incomplete pericardial sac. Bristowe describes a specimen which consisted of a rudiment of the pericardium at the upper and right side of the heart. In one case of incomplete pericardium, death resulted from dislocation of the heart during a severe attack of vomiting.

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CHAPTER III.

DISEASES OF THE MYOCARDIUM.

By ROBERT H. BABCOCK, M.D.

DISEASES RESULTING FROM DERANGEMENTS OF CARDIAC NUTRITION.

Both the functional and structural integrity of the heart muscle is dependent upon a supply of healthy blood, any abnormality in either the constitution or amount of which must affect it more or less seriously. In simple anæmia the heart may display weakness, dilatation, and increased frequency, whereas, in pernicious anæmia it may suffer degeneration. Again, autointoxication may probably be responsible for intermittency in its action, while the toxins of acute specific fevers are capable of producing structural changes of a most disastrous kind. It is, however, the mechanical interference with its blood supply from coronary sclerosis which is the most surely injurious, and it is the myocardial disease of this origin that is most frequently encountered.

Accordingly, whenever there is a structural defect with an insufficiency of the myocardium, it is usually found to depend upon a disorder of cardiac nutrition.

Etiology.—Acute Myocardial Degeneration.—*Acute Infections.*—For the most part it is the parenchymatous form of acute myocarditis which is seen as a result of acute infectious diseases. It is a manifestation of the action of toxins conveyed to the myocardium in the blood, and hence the likelihood of degeneration is proportionate to the intensity of the toxæmia and not its continuance (Romberg). Of the infections likely to lead to myocardial degeneration the most prominent are *diphtheria*, *typhus*, and *typhoid fever*. The involvement may declare itself during the course of the fever, but in many instances it becomes apparent only after the subsidence of the primary disease. It is also worthy of note that in the case of diphtheria the cure of the infection by antitoxin may not prevent the subsequent development of symptoms pointing to acute myocarditis.

Rheumatic fever, *scarlatina*, *variola*, and *influenza* are also capable of producing this form of acute degeneration. In the case of acute articular rheumatism, it is often the involvement of the myocardium rather than the endocarditis or pericarditis which renders the heart symptoms so serious. This has been well shown by the investigations of Poynton, who, in the microscopic study of a case that showed pericarditis during life, found extensive fatty degeneration of the muscle fibers with cell infiltration of the perivascular connective tissue. The injurious influence of *influenza* upon the heart muscle is a matter of every-day observation. Not only is the func-

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tional integrity of the organ disturbed in the course of the influenza, but signs of cardiac inadequacy may develop a considerable time after the disappearance of la grippe. An example was seen in a physician, who, a week or so after he considered himself fully recovered from an attack of influenza, developed tachycardia and moderate arhythmia with increase of cardiac dulness and muffling of the first sound at the apex. The danger to life arising from such a degenerative process makes the prolonged observation of the patient after convalescence from an attack of influenza highly important.

Gonorrhœa is also to be enumerated among the specific infections which may occasionally be responsible for an acute myocarditis (Romberg). The fact that gonorrhœal arthritis is purulent renders the myocarditis likely to be of the suppurative variety.

Toxæmia of Pregnancy.—It has come to be a recognized fact that parenchymatous degeneration of the myocardium is a not infrequent postmortem finding in women who have died during an attack of eclampsia. The lesion may vary from a cloudy swelling to a pronounced fatty degeneration. It is believed also that this condition of the heart muscle is responsible for the symptoms of cardiac insufficiency observed in pregnant women suffering from toxæmia, yet without convulsions. Bacon states that the symptoms pointing to this form of myocarditis occur in about 1 per cent. of pregnant women, a proportion greater than the percentage of convulsions.

Emboli.—Plugging of a coronary artery is another recognized cause of acute degeneration and inflammation of the myocardium. If it is benign, the result is an area of acute necrosis, but if, as is more frequent, the emboli are of a septic nature, abscesses result. Such septic infarcts may occur in the heart walls as a result of suppurative processes situated in remote parts, but are most common in the course of infective endocarditis.

Pyæmia may also predispose to septic myocarditis, and hence it was that gladiators in the time of Galen were so frequently found to have this form of acute myocarditis. The better surgical methods of to-day have rendered pyæmia comparatively rare, and hence abscesses of the myocardium are infrequent unless in the course of puerperal endometritis or septic endocarditis.

Coronary Thrombosis.—The enumeration of the causes of acute myocardial degeneration would not be complete without mention of coronary occlusion in consequence of thrombosis. As will be seen in the discussion of the causes of chronic degenerations, a coronary artery may become gradually thrombosed, in which event the nutrition of the heart suffers with corresponding slowness. When, on the other hand, the blood supply to an area is suddenly shut off, degeneration follows rapidly, or, in other words, acute necrosis results. Thus are provided the conditions which favor rupture and hence the extreme gravity of coronary thrombosis.

Chronic Myocardial Degeneration.—1. *Intrinsic Causes.*—The conditions which predispose to slow decay of the heart muscle are many and varied. Some of them are clearly understood and plainly apparent, while others are indefinite and difficult of satisfactory explanation. Belonging to the former class are all those factors which reside in the heart itself and hence may be called intrinsic. In the second are most if not all of the conditions which, existing outside of the organ, may be called extrinsic and which for the most part stand back of and are really responsible for the intrinsic ones.

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Coronary Sclerosis.—This is undoubtedly the one great intrinsic factor to which chronic changes of the myocardium are to be attributed. The sclerosis produces its effect on the heart muscle by its interference with the adequate supply of blood, not by the conveyance of toxins, although these may, in large part at least, be responsible for the sclerosis. The influence of coronary disease over the nutrition of the heart stands in direct relation to the degree of the sclerosis and the rapidity of its development. Thus, if the lumen of the arteries be gradually narrowed, the result is the development of fibrosis or fatty degeneration according to the degree of the coronary narrowing. If, on the contrary, a thickened and narrowed branch suffers sudden thrombosis, the result is, as we have seen, acute softening of the part supplied by that branch. Since a terminal twig possesses but a small caliber it may require comparatively slight thickening of its coats to induce thrombosis, and hence the frequency with which areas of necrosis are found in association with changes of a chronic nature in other parts.

It should be noted that cases are now and then met with in which, despite pronounced changes in the coronaries, the integrity of the myocardium does not appear to have been seriouly affected. In them we must assume either that the arteries were still capable of conveying sufficient blood for the needs of the muscle, or that the vessels of Thebesius were able to carry enough blood from the interior of the ventricles into the myocardium to prevent disastrous loss of its nutrition.

In certain cases, for example the so-called senile hearts, one is often astounded to find at autopsy such extensive and pronounced degeneration as to make him wonder how the organ managed to perform its function without clinical signs of greater inadequacy than actually existed. The explanation can only be found in the failure of the degeneration to involve the so-called vital centres, or the absence of other intrinsic factors, which, if present, would surely have served to overpower the organ.

Valvular Lesions.—These undoubtedly bring about degenerative changes in the myocardium in the course of time. Their mode of action is probably manifold, but the main factors are perversions of cardiac metabolism and increased work. Disturbance of the heart's nutrition results from lack of healthy blood on the one hand and defective removal of waste products on the other. Accordingly, all forms of valvular disease do not prove equally disastrous in their effects upon the heart walls. Aortic and mitral stenosis, especially the former, diminish the supply of blood sent into the coronaries because they lessen the amount discharged into the aorta; but in addition, mitral obstruction, through the stasis which it induces in the right heart, interferes with adequate flow from the coronary veins. Consequently it is in this form of valve disease that we meet with pronounced degrees of *brown atrophy.*

Regurgitant lesions on the left side of the heart also occasion myocardial degeneration in a similar manner, but as they would not appear to interfere so seriously with cardiac nutrition, at least in their earlier stages, they seem to exert their effect on the heart walls largely through the increased strain on them. This is particularly true of aortic insufficiency and hence it is in this affection that we sometimes see pronounced fatty degeneration of the enormously hypertrophied left ventricle.

The ventricle is called on for great increase of work, and at the same time demands increased nutriment both to maintain its nutrition *in statu quo*

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and to enable it to perform the extra work. If factors incident to its hypertrophy and dilatation prevent its receiving an adequate blood supply, then in time its fibers will undergo fatty degeneration. But, however, the degenerative changes in chronic valvular disease may be explained, they certainly are of greater importance in bringing about the final break in compensation than is generally recognized.

Heart Strain.—This is an element in the causation of chronic myocardial degeneration, but it cannot be clearly separated from other factors that bear directly or indirectly on cardiac nutrition. How heart strain, by which is meant excessive work, acts injuriously on the myocardium, and whether the injury thus produced can or cannot be separated from other malignant factors, are queries most difficult if not impossible to answer. It is likely that there must always be a disproportion between the demands on the heart and its supply of nutrition, if strain is to prove injurious. The healthy heart is capable of enduring enormous increase of work without obvious injury. If, however, the strain occasions dilatation and in particular hypertrophy together with dilatation, then conditions are seriously changed. Not only does dilatation augment the heart's work, but it also lessens the supply of blood to the coronaries, and in time these two factors, namely, increased work and decreased nutrition, occasion chronic degeneration. If hypertrophy co-exist, a greater amount of nutriment is required than normal, and if dilatation prevents this extra supply, myocardial degeneration will be inevitable.

From the foregoing considerations it becomes apparent that the intrinsic causes of chronic degeneration of the heart muscle all involve and presuppose a nutritional disturbance. Hence such factors are in their nature equivalent to disease of the coronary arteries, and in most instances are actually combined with sclerosis of these vessels.

2. *Extrinsic Causes.*—Some of these are plainly and unmistakably extraneous factors, while others are so intimately blended with the intrinsic causes enumerated as to make their separation impossible. Among the latter are the various conditions which necessitate prolonged and increased work. These will now be considered.

Mode of Life.—This includes a very comprehensive class, in which many elements work together, and overlap in a way which renders their separate discussion hardly advisable. The instances of chronic myocarditis, coming under this head, are those so frequently seen in large, ambitious, tireless men of affairs. They present clinical evidence of Fraentzel's idiopathic enlargement of the heart. That is, there are signs of hypertrophy and moderate dilatation, thickened arteries and excessive blood pressure, and generally, though not always, evidence of moderate interstitial nephritis.

The majority of such men have led a very strenuous business life, and in the majority of instances they have been good feeders, heavy smokers, and, perhaps, in the habit of taking wine or whisky daily, but in amounts which they considered quite moderate. In addition they have spent many hours of each day, for many years, sitting at their office desks, while business and social considerations have compelled them to attend frequent banquets, at which they ate, drank, and smoked more than was needful. A considerable proportion of these individuals have increased in weight as they neared middle age, this gain being shown chiefly in abdominal corpulence. Within certain limits, therefore Fraentzel's "luxus consumption" applies to their

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cases, since they persistently have taken a surplus of nourishment over the needs of their systems. This factor does not hold so true for them, however, as for some others whose excessive indulgence in the pleasures of the table leads to decided obesity.

In the class of individuals now described, this element of excess consumption is not a predominant one but is subordinate to or forms only one of a number of factors inseparably associated with their strenuous business careers. Modern business methods require men to work under high pressure and if this be kept up year in and year out some part of the organism must bear the brunt of the stress and strain, and at length begin to give way. In some men it may be the brain or nervous system, but in the persons now considered it is the circulatory apparatus. Long before the arteries show signs of thickening or the heart evinces pronounced hypertrophy there has been persistent high-pulse tension. It is probable that at this time the vessels within the abdomen have begun to undergo sclerosis in consequence of the abnormal blood pressure to which they have been so long subjected. There is, consequently, a very positive increase of peripheral resistance against which the heart must labor.

This being the state of things within the abdominal vessels, it is apparent that the sedentary occupation of the strenous men of affairs inevitably augments the danger threatening their hearts. By sitting for hours together at their desks, they deprive their hearts of the assistance to the circulation created by muscular exercise and deepened respiration.

There is still another most important factor which is commonly overlooked or under-rated in the discussion of cardiac hypertrophy and dilatation. This is the production of toxins within the intestinal canal and their absorption into the circulating medium. It is difficult to separate this subject from that of the harm which may result from defective elimination of catabolic substances by persons who lead a strenuous, business life and subordinate health to work. But independent of these products of tissue waste there are the toxins, which generated in the digestive tract under the influence of good feeding and sedentary pursuits, exert an injurious influence upon the nutrition of the arteries and myocardium.

We have come to recognize that a potent factor in the development of chronic nephritis lies in the strain put upon the kidneys by the elimination of toxins generated in consequence of faulty digestion. Sedentary occupation and excessive brain work are powerful elements in the causation of imperfect digestion, and consequent flatulent distention of the bowels. Many of these poisons are the products of putrefactive decomposition of animal proteids. These enter the circulation and have to be excreted, but in passing out of the intestines they enter the portal vessels and are conveyed to the liver. If not in too great amount they may be disposed of by this organ, but if they escape destruction in the liver they enter the major circulation and at length are carried to the kidneys. It does not seem at all unreasonable to assume that these poisons may thus be potent elements in the production of high and sustained pulse tension, either directly or indirectly. If they do not of themselves increase blood pressure they may exert their influence through the splanchnics, or they may induce degenerative changes in kidneys and arteries and thus help to augment the pulse tension.

It is also not a very great stretch of the imagination to assume that they may exert a directly injurious effect on the myocardium. It is not necessary,

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moreover, that individuals in whom such factors are at work should be conscious of indigestion. In fact, in their very unconsciousness of anything being at fault in their digestive apparatus, lies a great source of danger.

Alcohol.—This is a subject which is intimately connected with the considerations presented in the preceding paragraphs, and about which there is some conflict of views. No doubt exists concerning the injurious effect of excessive drinking, since fatty degeneration in the hearts of drunkards is a frequent postmortem finding. Moreover, the form in which their alcohol is taken seems important, as it is the drinkers of strong liquors, rum, gin, whisky, and brandy who develop fatty hearts. It would seem, therefore, that in the alcohol itself lies the injurious factor; yet to exert its baneful effects on the myocardium, it has to be taken in excessive amounts over a long period of years.

Immoderate beer-drinking, as in Bavaria, is held by German clinicians to produce disease of the heart muscle, yet not by reason of the alcohol so much as the vascular and cardiac strain incident to the absorption and elimination of many liters daily, in not a few instances as many as thirty, and to the relatively large quantity of nutriment contained in the beer.

On the whole, the writer is inclined to the view that the degeneration of the myocardium found in drunkards is not attributable so much to the alcohol as to impurities contained in the vile stuff they drink, for it is a known fact that men who drink only the best and purest whisky often consume a quart or more daily for a life-time without displaying more evidence of heart disease than do their strictly temperate brethren. It seems also that this matter of the abuse of alcohol cannot be separated from the evil effects of irregular habits in various ways; so that we may say the chronic myocarditis of old topers is to be attributed to the various factors entering into their mode of life, as well as to their intemperance.

Excessive Physical Toil and Hardships.—Considerable importance in the production of myocardial disease is attached to the severe physical exertion, together with the exposure and privations, experienced by soldiers, sailors, mountaineers, day laborers, coal miners, etc. Doubtless, the element of strain and malnutrition of the heart muscle comes into play in such individuals, but without question one cannot ignore the influence of many other potent factors entering into their lives, such as hard drink, irregular habits, and syphilis.

Chronic Infection.—This seems to be the place for the discussion of a factor which, experience has convinced the writer, is of immense etiological influence and which apparently is not generally recognized. This is chronic infection arising in the course of such diseases as cholecystitis and appendicitis. Without entering into details it may be stated that in a number of instances individuals who were sufferers from cholelithiasis or chronic appendicecal inflammation have complained of troublesome heart symptoms. In two cases of the latter kind the dilatation of the heart, detected prior to operation, wholly disappeared after convalescence, although the intermittence complained of did not vanish until a considerable time later, after the general health was improved. It may be argued that in such cases it is the effect of the local abdominal disturbance on the splanchnic system of nerves, and the consequent alteration in blood pressure which account for the cardiac disorder. The fact that in all the cases observed there has been leukocytosis suggests a different conclusion. In one instance, in a woman aged thirty-

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two, who died after an operation for cholecystitis of some years' duration, the coronary arteries were found atheromatous and the myocardium in a state of advanced brown atrophy. As no other cause for the cardiac degeneration could be discovered, it seemed reasonable to attribute this to the chronic gall-bladder infection. We know that arterial degenerations may follow and depend upon such acute infections as typhoid fever, and there seems no reason why changes in the coronaries and hence in the heart muscle may not equally well follow prolonged toxæmia of the kind seen in diseases of the gall-bladder and appendix.

Drugs.—It has long been recognized that fatty degeneration of the heart may result from phosphorus poisoning and the prolonged use of arsenic. These drugs act by injuriously affecting cardiac nutrition in the same way as they do the liver.

Exhausting Diseases.—Cancer, chronic dysentery, or other exhausting discharges, pernicious and even severe secondary anæmia, chronic suppurating diseases, all lead to myocardial degeneration. In pernicious anæmia the most extreme grade of fatty degeneration is often met with, while in protracted suppuration either this same form or amyloid change in the heart muscle may be found.

Morbid Anatomy.—Acute Changes in the Myocardium.—(*a*) *Acute Parenchymatous Degeneration.*—This condition is often spoken of as acute myocarditis, a term etymologically incorrect, since it implies an inflammatory and not a degenerative process. The condition in question results from the action of toxins generated in the course of acute infections. It is a diffuse process, characterized by cloudy swelling and granular degeneration of the muscle fibers. The myocardium accordingly looks pale and opaque, and is soft, flabby, and easily torn. Microscopically the fibers are seen to be swollen, their protoplasm more or less granular, and their striations are indistinct. They are fragile from fragmentation and segmentation, the rupture having taken place either through the cells or along their boundaries and probably having occurred during the death agony.

(*b*) *Acute Interstitial Myocarditis.*—This occurs in two forms, purulent or simple, depending upon the cause. The former is the result of septic emboli, while the latter occurs in certain infectious diseases, *e. g.*, diphtheria, and typhoid fever, and in connection with acute pericarditis.

Purulent myocarditis is characterized by septic infarcts of variable number and extent. Occasionally these abscesses rupture into the endocardium or pericardium. These foci of suppuration are usually multiple and vary in size from that of a pin's head to that of a pea. They appear as whitish or grayish areas which on section are depressed below the plane of the cut. Fluid or semifluid pus may be found in the larger abscesses, while the smaller are seen microscopically to consist of masses of polymorphonuclear leukocytes surrounded by a zone of degenerating muscle fibers. Bacteria may often be demonstrated in these areas.

The simple form is very rare and is characterized by infiltration of the tissue with lymphoid and plasma cells. There is also considerable degeneration of the muscle fibers shown by swelling and destruction of their nuclei. Foci of such changes are more numerous in the wall of the left than of the right ventricle, and are generally situated close beneath the endocardium.

(*c*) *Acute Necrosis.*—This is a form of acute parenchymatous degeneration which results from sudden occlusion of a coronary artery by thrombosis or

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non-septic embolism. It is variously designated anæmic necrosis, white infarct, acute softening, and myomalacia cordis. The degeneration is circumscribed and is most often found in that portion of the left ventricle and septum which is supplied by the anterior coronary artery.

The affected area has a yellowish-white or grayish-red color, is of irregular or wedge shape, and projects slightly above the surrounding level. The abrupt shutting off of the blood supply to the area leads to coagulation necrosis, which is soon followed by an inflammatory infiltration of the part. Microscopically these changes are shown by disappearance or fragmentation of the nuclei and by the invasion of leukocytes from the surrounding tissues. Ultimately this necrotic patch becomes transformed into a zone of scar tissue in the manner to be described under fibrosis.

Chronic Changes in the Myocardium.—(*a*) *Fibrosis, chronic interstitial myocarditis, fibroid degeneration*, are terms used to designate a condition in which the muscle fibers are replaced by fibrous tissue. The process may be diffuse, but is more often circumscribed. In the diffuse form there is a progressive atrophy of the muscle fibers with a corresponding increase of the interstitial connective tissue. When not very pronounced the condition is usually associated with a thickening or hypertrophy of the muscle wall. To the unaided eye the myocardium may, in the slighter degrees, look healthy, but when the fibrosis has led to thinning and dilatation, the heart is apt to have a paler appearance than normal and to cut with resistance.

In the circumscribed form of this degeneration there are smaller or larger areas of fibrosis, which in reality is a manifestation of nature's attempt to conserve the myocardium against the injury wrought by some antecedent process. Thus it may be the final or reparative stage of an acute degenerative change, as anæmic necrosis. The area becomes invaded by young connective-tissue elements which at length are converted into a firm fibroid cicatrix. The extent of such a focus is determined by that of the original lesion, but in most cases is not very great. To the naked eye such a fibrous patch appears as a yellowish-white streak or spot which projects slightly above the plane of section.

Foci of fibroid degeneration are most commonly found in the wall of the left ventricle not far from its apex, in the upper two-thirds of its posterior portion in proximity to the auricles, in the papillary muscles of the left ventricle, and in the interventricular septum. When not very extensive they may not seriously interfere with the functional integrity of the heart, but in some instances they lead to localized dilatation, as will now be described.

(*b*) *Aneurism of the Heart.*—Under this term is designated, not that bulging of the semilunar valves sometimes seen as a result of endocarditis, but a circumscribed thinning and dilatation of the wall resulting from fibroid degeneration. The condition is usually single but may be multiple. The pouching occurs most often at or near the apex of the left ventricle, since here is the most frequent seat of fibrosis. The aneurism may be of such small size as to scarcely merit the term or it may be so extensive as to constitute a sac of the size of the ventricle or of the heart itself. The pouch is very apt to be occupied by a thrombus, especially when it communicates with the cavity of the ventricle by a narrow opening. The formation of a coagulum within the sac is then conservative, as it tends to prevent rupture. In the

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vast majority of cases, however, the wall of the aneurism is unequal to the pressure of blood within it, and rupture takes place.

(*c*) *Fatty Degeneration.*—In this form of chronic myocarditis the heart muscle presents a generally pale appearance, with patches and streaks of yellowish-brown color, on which account it has been compared to a faded leaf or a tabby cat. The organ is much softer than normal, and can be easily penetrated by the finger. The areas of fatty degeneration are most common in the wall of the left ventricle near its apex, next in that of the right ventricle, in the interventricular septum, and in the wall of the right and left auricle in the order mentioned. The muscle close beneath the endocardium is affected by this form of degeneration more than that underneath the pericardium, and the brownish or yellowish area may sometimes be plainly seen from within the heart cavities. Microscopically the protoplasm of the fibers is found replaced by fat-drops arranged in rows and situated at the junction of the transverse and longitudinal striations. Very advanced fatty change of this kind leads to a disintegration of the muscle fibers, which may be replaced by fibrous tissue.

(*d*) *Rupture of the Heart.*—Fortunately this accident is rare, and yet it occurs with sufficient frequency to make its recognition important as a cause of sudden death. The conditions predisposing to rupture are fatty degeneration, an area of acute necrosis, a focus of suppurative myocarditis, extreme fatty infiltration, and even a gumma of the myocardium. Fatal hemorrhage into the pericardium has been known to follow rupture of a minute coronary aneurism. Rupture of the heart muscle takes place most commonly on the wall of the left ventricle near the septum, but may be situated in any portion of the organ which has undergone serious degenerative change.

(*e*) *Fatty Heart.*—This term is used to designate the fatty degeneration described above or an excess of adipose tissue. In well-marked cases of the latter kind there is an overgrowth of subepicardial fat which may cover the heart like a blanket and completely conceal the muscle beneath. It is the *cor adiposum* of old writers. There is also an infiltration of fat between the muscle fibers which in places have become atrophied or may be the seat of fatty degeneration. In extreme instances the heart is relaxed and its cavities are dilated. This increase of the adipose tissue of the organ is often combined with general obesity, but may be seen unassociated with corpulence.

It may be stated that when a heart is the subject of chronic myocarditis, it is very apt to present a picture which is made up of these varying conditions—fibrosis, fatty degeneration, and fatty overgrowth. As these changes depend upon disturbances in the nutrition of the myocardium, more or less evidence of coronary sclerosis is generally found. If there are associated changes in the kidneys and general arterial system, the heart is likely to be hypertrophied and dilated. In cases in which the sclerosis is most marked in or limited to the coronary arteries, the organ may be markedly atrophied and the myocardium really furnish a good picture of brown atrophy. This is seen especially in the so-called senile heart.

(*f*) *Fragmentation and Segmentation of the Myocardium.*—This condition, which was first described by French writers, has received much study by pathologists in Europe and America. Fragmentation is so called because the fibers are found fractured, the cells being broken at the level of the nuclei. In segmentation there is a separation of the fibers in their cement substance. The two conditions may be combined in the same specimen.

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This change in the myocardium may occur in the death agony or it may occur before dissolution, and prove a clinical and pathological entity of importance, although very difficult, if not impossible, of recognition during life. As we have seen, fragmentation and segmentation may be found in connection with fibrosis and other forms of degeneration.

Other Rare Forms of Degeneration.—(*a*) *Amyloid Degeneration.*—This is sometimes met with in the same class of cases as is this change in other organs. It occurs in the interstitial connective tissue and in the coats of the bloodvessels, but not in the muscle fibers.

(*b*) *Hyaline Transformation.*—This change in the fibers, first described by Zenker, may occasionally be seen after protracted fevers. The fibers are swollen, homogeneous, translucent and have nearly or quite lost their striations.

(*c*) Lastly, the muscle fibers may become infiltrated with lime salts and be the seat of *calcareous degeneration*, a condition which is very uncommon.

Symptoms.—Acute Parenchymatous Myocarditis.—These depend upon the nature and extent of the myocardial change. In one set of cases there may be no clinical evidence of its existence, and this is first discovered at autopsy. In a second group the presence of the disease is first declared by the sudden death of the individual. In a third class there are certain symptoms sufficiently pronounced to permit of its recognition by the attentive physician, while in still another set of cases there are symptoms due to the myocarditis, but they are obscured by, and are very likely to be referred to, some associated and easily recognized affection of the heart as endocarditis or pericarditis. On the whole it will probably be most satisfactory to consider the clinical manifestations of the disease under the head of the several acute infections in the course of which it occurs.

Diphtheria.—According to Romberg and Schmaltz, the symptoms of acute myocarditis make their appearance in from 10 to 20 per cent. of cases, and at any time from the close of the first to the fifth or sixth week, but most commonly in the second or third week after the attack. It is in this affection particularly that the existence of acute myocardial degeneration is first announced by the death of the child either when he is supposed convalescing satisfactorily or is thought to have recovered and has been permitted to resume his play. In one instance, a boy, aged seven who was supposed to be entirely well from diphtheria fell dead in the street while running. No autopsy was held, but in the light of his illness three weeks earlier, death was attributable to cardiac paralysis from myocarditis.

In the cases showing clinical evidence of this myocardial change there is increased frequency of the pulse with marked lowness of tension evinced to the palpating finger by emptiness and threadiness. Later on the heart's action becomes noticeably unsteady, so that upon very slight exertion the pulse grows rapid and perhaps irregular. This instability is in some cases the most characteristic and striking feature. At the same time there is apt to be a slight degree of cyanosis in consequence of loss of vasomotor tone, or the countenance may display conspicuous pallor and even anxiety.

Vomiting may occur and may be so marked a symptom as to give rise to the suspicion of serious gastric or cerebral involvement. The patient may be apathetic and listless or may display great anxiety and restlessness. Precordial pain is not a marked feature, there being a sense of dull ache or oppression rather than acute distress. It may be absent altogether.

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Examination of the heart at this time is likely to disclose great feebleness or even absence of cardiac impulse, increase of relative dulness transversely, and marked weakness of the tones. The first sound at the apex may be muffled and toneless, or it may be audible as a short, valvular tone which is accompanied by a more or less faint, blowing, systolic murmur. This murmur is generally restricted to the mitral area and denotes not an associated endocarditis necessarily, although such may be the case in other affections than diphtheria, but a so-called muscular mitral insufficiency.

This form of mitral incompetence is due to defective action of those various factors which normally produce effective closure of the mitral valve. In reality, therefore, it is a dilatation bruit which is heard, and hence it may wholly disappear after the cardiac asthenia has been recovered from and the left ventricle has returned to its normal size.

Signs of stasis are not so pronounced in the liver and other viscera as to attract special notice, and save for the pallor or the cyanosis the patient may not, to the inexperienced observer, betray by his appearance the serious state of his circulatory apparatus. On this account cases of grave asystolism are occasionally overlooked, and children convalescing from diphtheria are permitted to play about before the heart is equal to the exertion. It is probable that if the heart had been critically examined in the unexpectedly fatal cases it would have been found to display some of the features indicative of left ventricle weakness and dilatation.

Typhoid Fever.—In this affection, acute parenchymatous myocarditis is shown by emptiness and compressibility of the pulse rather than by marked frequency. The pulse rate is characteristically slow in proportion to the pyrexia and general feebleness. It may be this circumstance that serves to account in some measure, at least, for the want of conspicuous acceleration of its rate when the pulse is thready and weak.

The bedside recognition of this form of myocarditis is not easy, but in those cases in which it seemed to the writer to exist, greater rapidity of the heart's action was noted than is usual in typhoid fever, yet not so great as might have been expected in grave cardiac asthenia. The first sound at the apex has usually been strikingly wanting in clearness and strength, although an actual murmur was not detected. Careful percussion determined an increase in the area of deep-seated dulness often out of proportion to the clinical evidence of myocardial inadequacy. The objective manifestations of the myocarditis are to be sought, therefore, in the characters of the pulse and in the auscultatory findings rather than in venous stasis as in chronic myocardial and endocardial lesions.

Influenza.—The parenchymatous variety of myocarditis is evinced by increased frequency and feebleness of the heart's action as shown by the pulse and cardiac tones. This class of cases does not always manifest signs of heart weakness during the illness so much as afterward when the individual begins to return to work. If perchance the pulse may have been thought unnaturally weak and rapid during the acme of the attack, this has been attributed to the fever and prostration attendant upon the infection. It is found, however, that with resumption of active duties the individual is a little short of breath and not quite so strong as previously. He may experience also a slight or vague sense of discomfort rather than positive pain in the precordial region. Possibly, also, he is conscious now and then of palpitation or vertigo. His color is not good and at length he seeks advice.

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The pulse is found unduly accelerated, perhaps irregular in force and rate and possibly also occasionally intermittent. It is always of low tension both to the palpating finger and as shown by the sphygmomanometer. The impulse of the heart is feeble and the apex beat may be perceived as a light tap at or outside the nipple line. The tones are all enfeebled, especially the mitral first and the aortic second, while at the apex, particularly after hopping about the room, there is audible the short, faint, soft systolic whiff previously mentioned. This seldom wholly replaces the first sound and is always quite circumscribed to the mitral area. It is a murmur of dilatation, but denotes a muscular, not a relative mitral insufficiency.

Under rest in bed and appropriate medicinal treatment some of these patients recover their health and the heart no longer exhibits signs of inadequacy. In other cases the acute seems to pass into a chronic myocarditis, and the pulse never regains its former regularity and strength. The heart is permanently enlarged and there may be an apex murmur that bespeaks permanent damage to the ventricular wall or to the papillary muscles, and consequent incompetence of the auriculo-ventricular valve.

Acute Inflammatory Rheumatism.—The parenchymatous degeneration of the cardiac muscle is here very apt to be masked by the signs and symptoms of an associated injury of the endocardium. We know that when an acute endocarditis appears in children there is generally pronounced dilatation of the chambers most nearly concerned. We are wont to refer such enlargement of the heart to mechanical causes, but it is probable that pronounced dilatation does not occur unless acute myocarditis also exists. If the heart muscle is not seriously affected in its nutrition, a valvulitis is speedily compensated for by the development of hypertrophy in that division of the organ which has to bear the brunt of the strain. Therefore, when in acute rheumatism a degree of dilatation and asystolism develops which is disproportionate to the apparent endocardial mischief, acute parenchymatous myocarditis may be assumed.

If the heart walls are extensively damaged the rhythm of the contractions is likely to be disturbed. The pulse is apt to be accelerated rather than retarded, and to display more or less irregularity in time, force, and volume. Greater perturbation of the heart's action results from comparatively trivial exertion or mental excitation than should be the case. The patient becomes noticeably pale and may have an anxious look, yet questioned as to pain he denies this altogether or speaks of a dull, oppressive feeling at the heart rather than acute distress.

If such patients recover at all, it is only after weary months of scarcely appreciable improvement. Not only has the nutrition of the myocardium been affected, but that of the organism in general has been seriously compromised. In particular it is the kidneys which in these acute infections are likely to share in the inflammatory process. This is evinced by the appearance of albuminuria and casts. This nephritis disappears long before the myocardium acquires sufficient hypertrophy to denote a compensatory reestablishment of its power. Even then, after the individual has returned to his previous manner of life, more or less arhythmia is likely to persist, as a memento, so to speak, of the degeneration experienced by the muscle.

Acute Interstitial Myocarditis.—Cardiac symptoms are very likely to be masked by those of the underlying condition. When, however, the myocardial inflammation dominates the scene, the clinical picture is very like

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that of malignant endocarditis. There may be slight rigors, an intermittent pyrexia, and enlargement of the spleen. The heart's action is rapid and feeble and the area of cardiac dulness may be increased. The sounds are apt to be clear but weak, and murmurs are wanting. In some cases there may be nothing to indicate the critical state of the myocardium and the condition is recognized only at autopsy. In some of these cases the existence of the suppurative myocarditis is first revealed by the symptoms of collapse, the heart wall having ruptured into the pericardium. If an abscess has broken through and discharged its contents into the blood stream, there are the phenomena of septic infarcts in distant parts, skin, kidney, spleen, liver or brain, as the case may be.

From the foregoing it is apparent that when viewed from the standpoint of its symptomatology, acute myocarditis of either form may be divided into two classes: (1) In which symptoms pertaining directly to the heart are either absent or so obscure as to be overlooked; and (2) cases in which evidence of cardiac incompetence is too conspicuous to be overlooked or may be discovered if sought for.

For the most part it is the first class of cases which are especially dangerous and for the discovery of which the physician should be always on the lookout when treating any case of acute infection. He must not be deceived by the want of obvious signs of venous stasis, for these are more apt to be absent than present. The reason for this is conjectural. It may be due to toxic paresis of the vasomotor centres as suggested by Romberg, or under the influence of a splanchnic neuritis (Veronese) there may be stasis within the great veins of the abdomen with corresponding emptiness of the arterial system.

The physician is to be on the watch for slight yet significant signs of myocardial weakness. These are feebleness and emptiness of the pulse rather than marked frequency; perturbations of rate and rhythm out of proportion to the degree of effort that evoked them; sudden and alarming periods of weakness when the pulse grows rapid and almost imperceptible; listlessness and weakness on the part of the patient and apathy or marked restlessness. Striking pallor of the countenance, vomiting, and precordial pain are symptoms which, if not always present, are yet very significant and should excite apprehension. If combined with some of the evidences of myocardial incompetence described, they render the existence of acute myocarditis highly probable.

The *course* of the disease may be quite diverse both as regards onset and duration. It may set in suddenly and under symptoms of ever-increasing severity lead to death in a few days or weeks. On the other hand the myocarditis may develop insidiously and remain latent up to the moment of unexpected death; or there may be periods of entire absence of symptoms which alternate with times of alarming asystolism and all the appearances of impending dissolution. Lastly, it is important to remember that the affection may first declare itself by signs of cardiac inadequacy of greater or less severity, several weeks after all thought of danger has passed.

Chronic Myocarditis.—There is much diversity in detail presented by the clinical picture of chronic myocardial degeneration, yet different as these points of contrast may be, the background remains ever the same, namely, cardiac incompetence. The differences are determined by the seat and extent of the morbid anatomical changes as well as by their

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exact character and their association with degenerative changes in other organs. Cases falling under this head may be variously classified according to their pathogenesis, their pathological peculiarities, or their clinical manifestations. An etiological grouping would be very desirable, but seems impracticable in the present state of our knowledge, since we are not able to decide which of several factors may be the essential one. A classification based upon the precise nature of the myocardial change is likewise not feasible since various changes generally exist in each case. We are confined, therefore, to a division of cases based on their clinical manifestations, and on the whole this appears to be the most useful.

Two main groups of cases may be distinguished: (1) Those in which symptoms referable to the heart are latent or so disguised as to escape recognition, and the existence of heart disease is first declared by sudden death; (2) those in which symptoms of cardiac inadequacy are more or less conspicuous. The cases making up this second group may be subdivided according as symptoms are distinctively cardiac or are blended with others attributable to disease of other structures than the myocardium. In reality it is the union of several such interdependent conditions which accounts for the diversity in the details of the clinical picture. Accordingly, in the following description this arrangement of cases will be maintained so far as is compatible with clearness and accuracy.

Latent Cases.—In this group belong the occasional instances of sudden and unexpected death occurring among middle-aged or elderly and apparently robust men. They are very apt to be reported as cases of apoplexy, but are in reality instances of cardiac paralysis or sudden heart failure. The Germans call it "herzschlag" (heart stroke), and appear to recognize its exact nature more often than is done in this country.

In instances of this kind it may be that a man engaged in conversation or perhaps at the end of a meal, in whom nothing abnormal has been noted, falls over dead. In the press reports of these cases it is generally said that the deceased was in excellent health and had experienced no symptoms that indicated to his friends the existence of heart disease. Such is doubtless true in many instances. In others there have been symptoms which were attributed to indigestion, nothing more. It is quite likely, nevertheless, that if these victims had been critically examined they would have exhibited to the skilled observer some of the signs which point significantly to the probability of chronic myocarditis.

The reasons for the latency of these cases are to be found in the insidiousness of the changes going on in the heart muscle and in the location of these changes. Their seat may be in the septum, so as to involve that portion (the coördinating centre) whose integrity, as is well known, is essential to life and which, therefore, is a vital centre (Kronecker and Schmey). Under such circumstances, as pointed out by Huchard, degeneration of this centre renders sudden death liable at any moment.

On the other hand there may be a condition of hypertrophy with dilatation of the left ventricle, the former condition having predominated for years and thus precluded subjective symptoms. The degenerative process slowly and insidiously saps, however, the strength of this hypertrophied wall, and at length it becomes incapable of withstanding high intraventricular blood pressure. So at length comes a moment when under the inhibitory stimulus of some strong emotion, an unwonted or hasty physical effort, a

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hearty meal, etc., blood pressure within the degenerated ventricle is raised to an insupportable degree and the heart stops in diastole.

Such a time of danger may arise in the life of any person whose myocardium has become degenerated.

It occurred in the case of the writer's grandfather, at the age of eighty-seven, when he was seemingly as well as usual and directly after he had returned from a walk down town, as was his daily wont. But in such an old person sudden death is scarcely a matter for surprise, since we expect their hearts as well as other organs not to be sound. In the class of cases now under consideration, however, sudden death comes as an awful shock because of the activity and apparently unimpaired vigor of the individual.

Examination of the heart in these latent cases would probably reveal signs of general cardiac hypertrophy. Although by reason of the capaciousness of the chest the area of heart dulness may appear natural, still the increase of pulse tension and the slight thickening of the arterial coats evince the strain to which the heart has been subjected, while the intensity and ringing quality of the aortic second tone bear confirmatory testimony.

It is also very possible that in these cases there is more or less acceleration of the pulse, or a slight amount of breathlessness on exertion to which the individual pays no heed, having attributed it to his increasing weight or age and, therefore, supposed it quite natural. Such, at all events, are the evidences of incipient, cardiac incompetence which may be detected in men who considered themselves in perfect health.

Cases with High-tension Pulse and General Cardiac Hypertrophy.—It must not be supposed that the cases grouped under this head monopolize these features of the pulse and heart. They only constitute the findings which stand forth most prominently in the examination of these cases. Fraentzel designated them idiopathic enlargement of the heart to distinguish them from instances of hypertrophy secondary to chronic valvular disease. In the writer's experience they are most commonly found among the large-framed, energetic men who were described under Etiology as engaged in office work and under the influence of good living, early develop a degree of abdominal corpulence which puts an injurious burden upon their circulatory apparatus.

Slowly and insidiously the myocardium has been answering to the heavy demands made upon it by ever-increasing thickness of its walls, not a true hypertrophy of its muscular elements, but a false hypertrophy in consequence of the growth of connective tissue. To whatever special factors the augmentation of blood pressure is to be ascribed in these cases, the fact remains that for an indefinite time there has been high and sustained pulse tension. There may or may not be demonstrable thickening of the arterial coats, and some degree of renal change may be shown by urine containing a few granular and possibly hyaline casts. Now and then a trace of albumin may be detected, but on the whole the renal elimination is satisfactory.

Year by year the elevation of blood pressure becomes more pronounced, and little by little the development of fibrous tissue undermines the resisting power of the myocardium. At length symptoms begin to declare the strain to which the heart is slowly yielding. In some cases it is *dizziness* which first attracts attention. The sensation is slight and transient, perchance, but it occasions uneasiness, and a physician being consulted, the state of the heart and vascular system is recognized. Remedies are prescribed for

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diminution of pulse tension and the patient is relieved of his annoying vertigo. In some instances the excessive blood pressure leads to a severe and almost uncontrollable attack of epistaxis, and thereafter symptoms are relieved for a time.

In other cases it is *breathlessness on exertion* which is first noticed. This too may be lessened or removed for a time, but, as a rule, it does not vanish altogether. Associated with the shortness of breath may be a sensation of weight or *fulness in the precordium*, or there may be a dull ache or pain in the upper cardiac region whenever the man walks at more than a very moderate pace.

In still other cases the initial symptom which takes the patient to a physician is *palpitation*. It is often described as a thumping or pounding of the heart which attracts notice during exertion or at night. In some instances the individual is unable to lie on his left side because of this sensation. Not infrequently breathlessness is experienced as well as palpitation or vertigo. In other cases the patient complains chiefly of *epigastric fulness* or pain which he attributes to indigestion. His conviction of its being only a digestive disorder is increased by the fact of eructations or by aggravation of his sensations after meals. If he is a little short of breath, especially after eating, he regards it as due to bloating with wind.

In some one of these various ways this type of myocardial incompetence first makes its advent known. As time goes on, however, the degree of cardiac inadequacy increases and the individual finds himself attending to his ordinary duties with ever-growing difficulty. Usually at this time it is the shortness of breath which incapacitates him. He is aware of decreasing strength and endurance, but it is the dyspnœa which really torments him. He is noticeably short of breath even when at rest in his chair, but it is when he walks about or when he goes to bed at night that he suffers the most. Thus, things go on from bad to worse and at last he gives up and stays at home.

Examination of the heart now discloses plain signs of myocardial incompetence. The pulse is more or less accelerated, usually regular and of high tension. The palpating finger finds it difficult to compress the artery and the sphygmomanometer registers anywhere from 160 to 200 mm. Hg., or in exceptional instances even higher. The radial arteries roll under the finger but are not generally markedly sclerotic. There may or may not be puffiness, or even pitting of the ankles.

The apex beat if perceptible is found in the fifth intercostal space, and on the nipple line or somewhat outside, but by actual measurement from four to five inches to the left of the median line. There may be epigastric pulsation of variable strength according to circumstances. Deep-seated and superficial dulness is increased in all directions but chiefly to the left, and the outline is quadrangular, indicating general enlargement. The heart sounds are somewhat enfeebled, especially the mitral systolic, which is often accompanied by a soft, blowing murmur. The pulmonic second tone is likely to be accented and the aortic second sound is ringing in consequence of the high blood pressure.

The lungs are resonant, but at the posterior bases, rales of chronic bronchitis or hypostatic congestion are heard. Now and then there may be a slight amount of fluid in the right pleural cavity. The liver is enlarged, as shown both by palpation and percussion. The urine is diminished in amount,

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of increased specific gravity, and may contain a variable percentage of albumin. If casts are present they are granular, or both granular and hyaline.

The course of the disease is henceforth either steadily from bad to worse, or, under treatment, tends for a time to general improvement. In the former event, œdema increases until general dropsy supervenes; the dyspnœa becomes orthopnœa, with possible paroxysms of veritable air-hunger. The heart grows more and more incompetent with possible irregularities in force and rhythm. Hepatic stasis augments even to the point of epigastric pain and tenderness. The lungs grow distinctly œdematous, and the urine is scanty and highly albuminous. The clinical picture has now become that of extreme myocardial insufficiency from whatever cause. The end to the struggle comes slowly and gradually, or, after weary months, the worn-out heart stops suddenly as the patient rises from his chair or completes the act of micturition or defecation.

Should treatment, on the contrary, improve the patient's condition, the reinstatement of heart power is but partial and often transitory. In the case of a rich man, a journey to Bad-Nauheim is succeeded by such a gain in strength that he is able to return to his office the following winter. Or, the less fortunate workingman finds so much relief from his symptoms to result from rest in bed in a hospital ward, that when he is finally discharged he flatters himself he can resume his arduous vocation. In either case the man sooner or later again grows conscious of the insidious approach of his old enemy. This time the symptoms, if they yield to treatment at all, do so with greater reluctance than before. Thus, with discouraging repetitions, the patient drags on until death terminates the unequal fight, either abruptly and unexpectedly, or in the midst of all the phenomena which mark extreme myocardial inadequacy. In not a few instances it is a secondary pneumonia which closes the scene.

Cases Associated with Chronic Nephritis.—In the class of cases just depicted the urine is not normal, but if the kidneys are diseased their condition is wholly subordinate to that of the heart. In those now to be described the primary disorder is a chronic nephritis, commonly of the interstitial variety but many times of a mixed kind. There has been abnormally high tension for years, which, directly prior to the breakdown, may reach the enormous figures of 225 or even 260 mm. It is this excessive peripheral resistance which is responsible for the failure of myocardial hypertrophy, and when at last serious symptoms set in they are in reality those of cardiac rather than renal incompetence, although the latter supervenes in time.

Usually the first symptom to rivet the patient's attention is shortness of breath on exertion. In some cases it is vertigo which appears while the man is walking in the street. As time goes on this breathlessness grows into outspoken dyspnœa. It is apt to be associated with unwonted nervousness and more or less decrease in strength. Some patients suffer to such a degree from dyspnœa, nervousness, and insomnia that their days and nights are a series of unendurable torture. In restless search for relief they tramp and work until utterly exhausted, and then go to bed in hope of repose. Before long, however, the dyspnœa forces them to spring out of bed gasping and panting for air.

If the heart is examined at this time, it is found hypertrophied and beating with increased frequency in the attempt to overcome the resistance offered

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by the abnormal pulse tension. The sounds may be clear but there is often the short, blowing, apex murmur which, accompanying the mitral first tone, denotes muscular insufficiency of the valve. The aortic second sound is loud and ringing, and in some cases is the most marked feature in the examination. Accentuation of the pulmonic second tone indicates the heightened blood pressure in the pulmonary vessels, but other signs of congestion within the lungs are not very manifest. Evidently it is the excessive pressure in the aortic system which is overpowering the myocardium. The hypertrophied heart is struggling to preserve its potential integrity against insuperable odds.

Appropriate treatment ameliorates the sufferer's condition for a longer or shorter period. Yet, if examined from time to time, the pulse is found habitually tense and too rapid. Hypertrophy still predominates, but is slowly yielding to dilatation. There are no pronounced cardiac symptoms, and yet he is aware, every now and then, of breathlessness or palpitation and of a want of his old-time vigor and endurance. At length, either in consequence of injudicious physical effort or because the degenerated myocardium has yielded to the dilating force of the persistently high-pulse tension, the patient's dyspnœa reasserts itself. From this point forward the symptoms are those of myocardial incompetence.

Examination of the heart now shows a combination of hypertrophy with dilatation which is apt to involve chiefly the left ventricle. The area of deep-seated dulness is not quadrangular as in the preceding group of cases, but extends to the left to a variable distance outside the nipple line. The apex beat is diffused and uncertain, and the palpating hand appreciates an indistinct doubling of the impulse. Upon auscultation, this diastolic tap is found to correspond to a reduplication of the second sound, which imparts to the tones a more or less characteristic gallop rhythm. There may or may not be also a systolic apex murmur depending upon the degree of dilatation.

The pulmonic second sound is intensified and the aortic is diminished, but more sharp and metallic. The pulse is of increased frequency, 110 to 125, and regular or now and then faltering or intermittent. The radial artery is hard to compress. The sphygmomanometer still records hypertension. The liver is apt to be palpable and may be tender. In many cases it is firmer and thinner than in pure congestion of the organ. As proven by the subsequent history, it is cirrhotic. The urine is less abundant than formerly and usually contains albumin and casts. The ankles may pit slightly, but in the beginning of this final struggle are not markedly œdematous. In some instances dropsy is now wholly wanting.

The course is now very like that in any other case of cardiac inadequacy, but the patient's dyspnœa, restlessness, nervousness, and increasing weakness are apt to be more pronounced than in the incompetence of valvular disease. Under the combined influence of powerful cathartics, a restricted dietary, and the inherent tendency of the albuminuria, the patient gets into a state of hydræmia which results in general dropsy and, finally, ascites.

Not infrequently this state of malnutrition brings on acetonæmia or a form of toxæmia which is an *inanition toxæmia*. The patient is not actually delirious but is drowsy and not clear in his mind, while at night he may actually show mental rambling and sometimes excitement. In some cases the toxæmia is of an *hepatic* origin and closely simulates urænia. The breath is heavy

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and foul, and the sensorium is decidely obscured. Occasionally the breathing may assume a Cheyne-Stokes type.

The heart is now still more dilated; a tricuspid, regurgitant murmur has become added; the external jugulars pulsate visibly; the liver is still more engorged; the pulse is irregular, intermittent, or too arhythmic to be accurately counted. It is feeble and the sphygmomanometer now shows an abnormally low tension 105 or even 90 mm. The state of things is truly pitiable and the fatal termination of the case is only a question of time. Death may come suddenly when the patient seems in the same condition as for many weeks, certainly a very merciful ending, or the feeble spark of life may simply flicker out; or uræmic coma may terminate the struggle; or the exitus may take place in consequence of pulmonary œdema. Autopsy reveals extensive degeneration of the myocardium in connection with the primary and secondary change in the kidneys and other organs.

Some of these nephritic cases show wonderful tenacity of life so far as the heart is concerned. According to the writer's experience they are those which display predominating dilatation of the right heart. The left ventricle is also dilated and the mitral valve leaks, but the behavior of the organ as a whole points to degeneration and stretching of the walls of the auricles and right ventricle as the leading feature. The action of the heart is so arhythmic that one can aptly apply the term, delirium cordis.

The excretory ability of the kidneys is greater than might be supposed from the degree of albuminuria, and they often respond well to such a remedy as diuretin. But the drain on the system tells surely though slowly, and the anasarca is largely hydræmic, as shown by the softness of the tissues on pressure. Nevertheless, it is the myocarditis even more than the nephritis that is surely dragging the patient to his grave. Part of the clinical picture is owing to the albuminuria, it is true, but it is the incompetence of the heart muscle which is mainly responsible for the dyspnœa. That it is not stasis, solely, which causes the dropsy in all cases, is proven by its diminution or disappearance after chloride of sodium has been withdrawn from the dietary.

In not a few instances the œdema is so slightly influenced by a non-chloride diet that venous stasis must be regarded as a principal factor in its production. It is these cases that are so intractable to treatment, and which pursue a steadily downward course and terminate in months at the outside. There is a vicious circle of conditions which precludes all hope of recovery, but the fact that other than palliative measures are without avail from the moment the abnormally high gives way to low blood pressure, proves that the chronic myocarditis has become the reason for our defeat, if, indeed, it were not so from the outset.

Cases with Angina Pectoris.—A relatively small number of cases display, as their leading feature, more or less typical attacks of Heberden's angina. In strictly classical examples of this, the heart may display some degree of hypertrophy and the aortic second sound is clear and ringing, but more obvious departures from health are seldom present. The radial arteries may be sufficiently stiff to roll under the palpating finger, but the pulse may not show marked tension and be quite regular. This form is most often seen in elderly men, and the condition primarily responsible for the anginal seizures is sclerosis of the coronary arteries. The myocardium is secondarily affected, but is still competent so far as can be measured by symptoms. When under favoring conditions the patient can walk without pain, he is not

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conscious of dyspnœa and often declares he would be perfectly well were it not for his anginal attacks.

There is another form in which evidence of cardiac incompetence is so plain as to warrant the diagnosis of chronic myocarditis. The attacks of pain may not be exactly typical, and yet are sufficiently so to render clear in what category they belong. The heart is found dilated and feeble; its action is too rapid and is irregular, although not always very arhythmic; the sounds are weakened, the aortic second being accented and there being a systolic murmur in the aortic and, perhaps, also in the mitral area. Such a patient presents more or less shortness of breath, although this is quite apt to be ignored in consequence of the greater impression made by the angina. There may be a demonstrable engorgement of the liver, and impaired resonance with subcrepitant rales may be discovered at the base of the lungs behind. The urine may or may not show albumin and casts, but for the most part chronic nephritis is a minor consideration. The peripheral arteries are moderately sclerotic, and pulse tension is raised.

In the former type of cases the angina pectoris dominates the clinical picture up to the end, which is very apt to occur with more or less suddenness. The second class of cases may likewise terminate by sudden death, but in some instances the symptoms of myocardial inadequacy increase until they display, to a greater or less degree, the characters portrayed in the preceding groups.

Cases of the Senile Heart.—One not infrequently encounters old people of both sexes whose hearts, if examined by the pathologist, would display the changes of myocardial degeneration, yet who enjoy a state of health that is truly surprising. The pulse is more or less irregular and sometimes so arhythmic as to startle the physician. Its tension is increased to 145 or 165 mm. Hg., and the arterial coats feel stiff or even beady. The apex beat is displaced outward and downward in consequence of combined hypertrophy and dilatation. The sounds are accompanied by systolic murmurs both at the apex and in the aortic area, while the second tone is ringing and possibly impure. The urine shows changes that go with this cardiovascular degeneration, namely, nocturnal increase, low specific gravity, a trace of albumin at times, and granular and sometimes hyaline casts. Stasis in the portal vessels is not marked, but digestive disorder shows itself by flatulent distention of the bowels and eructations.

The majority of such old persons keep tolerably well so long as they follow the even tenor of their way. So soon, however, as they overdo in some manner, and, particularly if they contract a bronchitis or some other ailment, as a diarrhœa ordinarily trifling in the robust, they show at once how little resisting power they possess. The heart at once evinces its intrinsic feebleness, which it is important to recognize speedily and endeavor to arrest before it grows more serious. These patients are very likely to succumb to pneumonia or influenza. In many of the cases the chronic myocarditis is but an incident in the advent of old age, and, so long as the heart is potentially equal to its ordinary work, it requires nothing more than protection against additional demands. In other cases distinctively cardiac symptoms may make their appearance and pursue the usual downward course. In not a few instances these old hearts rally in a wonderful manner, under skilful management, and then may be bolstered along for months and even several years.

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Cheyne-Stokes respiration may appear and persist in a more or less typical form. In other instances it may disappear after a time or show itself only when the patient is asleep. It does not depend upon the state of the myocardium so much as upon the condition of the vessels in the medulla, and hence the blood supply to the respiratory centres.

Precordial pain may or may not be experienced, but in the cases considered typical illustrations of the senile heart it has been the exception. In a few instances angina pectoris has been a leading feature and in others there has been a dull pain in the cardiac region, which, however, was subordinate to other symptoms.

The *pulse* presents all possible variations in rate and rhythm. It is more apt to be too frequent than too slow, and there may be paroxysms of tachycardia of uncertain duration. When these subside they leave the patient much exhausted. They may be an expression of cardiac asthenia and after several months of treatment the pulse, previously very weak and arhythmic, becomes regular and fairly strong.

Irregularity of the heart's action is a marked feature of many cases, presenting such a loss of rhythm that it is aptly described by the term delirium cordis. In other cases irregularity of the pulse shows itself only during some physical effort as walking and then evinces the potential feebleness of the myocardium.

Cases Presenting the Stokes-Adams Syndrome.—Abnormal slowness of the pulse, to which earlier writers used to attach so much importance in the diagnosis of fatty degeneration of the heart, is far less common in chronic myocarditis than is increased frequency. The cases in which the writer has observed habitual bradycardia were in middle-aged men with general enlargement of the heart, such as have been depicted in the second group. Now and then a case is encountered in which the myocardial incompetence is attended with paroxysms of recurrent bradycardia of such striking character as to merit a separate clinical grouping.

These cases are marked by recurrent spells, which, originally described by Stokes and Adams, have been named after these eminent Irish observers. These attacks are characterized by recurrences of such extreme slowness of the heart's action that the brain is inadequately supplied with blood, and hence the individuals suffer also from vertigo or even syncope. In some instances the seizures so closely simulate an epileptic fit, that they have been mistaken for convulsions of this nature. Although not confined to persons of middle or advanced age, still these attacks of recurrent bradycardia are most often seen in individuals whose various organic lesions, if not their actual age, place them in the category of senility. These patients usually, but not always, die suddenly, probably from heart block during one of their attacks.

Cases of Rupture of the Heart.—Chronic myocarditis occasionally terminates abruptly through rupture. The mishap is announced by symptoms denoting grave cardiac failure; precordial pain or oppression, rapid, feeble pulse, cold extremities, and pale, anxious countenance, in short, the symptoms of collapse. The area of heart dulness is increased, and the tones are distant and weak. Death supervenes after a shorter or longer period, from a few minutes to many hours, and a correct diagnosis is usually made only at autopsy.

Cases of Aneurism of the Heart.—Symptoms by which this condition may be recognized are rarely occasioned. Such as exist are attributable to myo-

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cardial inadequacy. A lawyer whose coronary arteries were atheromatous and the apex of whose left ventricle was bulged out into an aneurism and filled by a clot the size of a small English walnut, displayed persistent tachycardia and symptoms of asystolism. After this state of things had endured for about two months, he fell to the floor and expired immediately subsequent to the act of micturition. If the aneurism be very large it may so modify the outline of cardiac dulness as to lead to a correct diagnosis. In very rare cases there may be bulging of the chest wall in the vicinity of the apex, and this tumor may pulsate so as to simulate a double apex beat. The symptoms are in effect those of cardiac dilatation, and the case ordinarily passes for one of chronic myocarditis.

Cases Simulating Valvular Disease.—It is not very uncommon to encounter individuals of forty or over who manifest symptoms of cardiac insufficiency, and who, on examination, are found to have signs of mitral or aortic valve disease. Sometimes it is a mitral regurgitation, sometimes an aortic leak, and occasionally there is evidence of slight stenosis associated with the incompetence of the mitral valve. There is no clear history of acute inflammatory rheumatism, but there is often a statement of some antecedent strain. As in a patient now under observation, there is history of unwise and excessive physical effort together with fairly good evidence of irregular heart action for a number of years prior to the arduous mountain climbing which precipitated the present breakdown. These cases present nothing especially peculiar in their symptomatology, but should be carefully studied with a view to ascertaining the state of the heart muscle. Pulmonary œdema occasionally occurs in these patients.

The prognosis and, to a certain extent, the nature of the treatment depends upon the degree of damage sustained by the myocardium. Thus the writer treated a man of forty for several years under the supposition of his free mitral regurgitation having originated in rheumatic endocarditis, the history of rheumatic attacks being quite definite. When at length the heart gave out it did so in a very short time, but not abruptly. The autopsy disclosed no changes of the valves, but an extreme grade of fatty degeneration. This had permitted dilatation during life and consequent reflux through the left auriculo-ventricular orifice.

Instances of aortic insufficiency, of the kind now considered, are in reality secondary to degenerative changes in both arteries and heart. They may be quite appropriately regarded as a part of a general decay of the circulatory apparatus, yet their development is so insidious that recognition of the leak generally takes place after its complete establishment, and compensating hypertrophy has occurred. In several such instances the myocardium has been found so degenerated as to really bring the cases in the category of chronic myocarditis rather than in that of valvular disease.

Symptoms in these cases of pseudo-valvular lesions are of the kind seen in failing hearts from whatever cause, but there are generally clinical data pointing to degenerative changes in the arteries, kidneys, and liver which assist in the *intra vitam* recognition of vascular and myocardial decay as the fundamental condition. Such cases are extremely common among negroes in whom they probably have a syphilitic origin.

Symptoms of the Fatty Heart.—There are undoubtedly cases of fatty overgrowth and infiltration which deserve the term *fatty heart* or *cor adiposum*, but it is an error to suppose that all obese individuals have this kind of a

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heart. It is likewise erroneous to infer that corpulent persons exhibiting signs of myocardial incompetence necessarily have fatty hearts. Furthermore, a heart that is enveloped in a thick layer of adipose tissue may yet be capable of performing its functions without evincing special weakness. These considerations render the term fatty heart objectionable, from a clinical standpoint. It would be far more in accordance with facts to adopt the term, *myocardial incompetence of the obese.*

The symptoms observed in this class of cases are not peculiar, but are essentially those of cardiac inadequacy from other causes. When they arise it is usually in consequence of the heart's inability to longer endure the heavy strain imposed upon it by the obesity. Not only is the work of the organ magnified by reason of the individual's weight, but the new vascular areas which have been developed for the supply of nutrition to the excessive layers of fat, put additional burdens on the central organ of circulation. The heart is required to do an extra amount of work that is commensurate with the degree of obesity. Some corpulent individuals, moreover, are anæmic and the myocardium is inadequately supplied with nourishment. This is one reason why some fat persons develop symptoms of cardiac incompetence at a comparatively early age. Then there is another class of fat and plethoric individuals who have good musculature and are remarkably energetic and active, seeming to pride themselves upon their ability to outrun and outwork much lighter persons.

The fat and anæmic are in danger of overtaxing their hearts by unusual exertion, but warned by their shortness of breath rarely commit acts which seriously overstrain their heart walls. The fat and muscular, on the other hand, often subject their hearts to enormous strain and consequently form the class in which myocardial insufficiency is the more frequently seen. If the arteries are stiff, or if blood pressure has been high for many years in consequence of excessive intra-abdominal blood pressure, chronic nephritis, etc., the myocardium may be in a state of degeneration and hypertrophy. In such a case the condition is in reality a chronic myocarditis, not a fatty heart.

In a minority of cases the heart is neither fatty nor degenerated; it is simply inadequate because of the disproportion between its potential strength and the burdens it has to carry. The organ has hypertrophied to its limit and then being unable to hypertrophy further, it dilates. This is the first step in its downward career, and now distinctive symptoms make their appearance.

Breathlessness on exertion is so usual in corpulent individuals that it is lightly regarded by them. Now, however, myocardial incompetence causes them to puff and blow in a way quite unusual, and upon relatively slight exertion. Dyspnœa is now fully established and in some instances may be fairly constant. From this time on to the end it remains a marked feature.

The pulse is increased in frequency and regular or irregular as the case may determine. Its tension is usually augmented in the beginning, but tends to fall with progress of the inadequacy. In cases in which chronic myocarditis, secondary to renal disease or excessive intra-abdominal blood pressure, does not co-exist, the tension of the pulse may not be noticeably raised even at the commencement of subjective symptoms.

Examination of the precordium is generally unsatisfactory. The cardiac impulse is not perceptible on account of the *panniculus adiposus*, and for the same reason it is difficult to obtain definite data by percussion. Ausculta-

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tory percussion may enable one to obtain a fairly reliable outline of the area of dulness. Upon auscultation the sounds are distant and feeble, and murmurs are generally not audible. Careful attention may detect special feebleness of the first tone at the apex, and accentuation of either the pulmonic or aortic second sound. It is possible also that after the patient has been required to hop about the room, or to ascend a flight of stairs, a soft blowing murmur may develop in the mitral area. This sign, which is so commonly elicited in cases of myocardial insufficiency, is an exceedingly important finding, since it indicates the degree of dilatation of the ventricle occasioned by exertion.

As a rule, fat people rarely exhibit as marked evidence of turgescence of the superficial vessels as do thin individuals. Indeed, capillary stasis may only give them a ruddy or plethoric appearance which may be mistaken for the hue of health. It may quite disguise the degree of anæmia actually present. The abdominal corpulence also prevents palpation of the liver, and hence stasis in this organ may not be detected. Puffiness of the ankles may be present in the beginning, and as circulatory activity decreases may at length merge into actual œdema. The urine may present the changes of renal stasis or nephritis, or both, while flatulent distention of the stomach and bowels adds to the patient's discomfort. In brief, the clinical picture is that of more or less extreme heart failure. The background of the picture is ever the same; it is only the details and coloring which are different, and these are determined largely by the degree of obesity.

Diagnosis.—Acute Myocarditis.—Not only is the determination of the existence of this affection a matter of difficulty and often of uncertainty, but the physician must endeavor to decide which form is present. He should never lose sight of the possibility of acute myocarditis in the course of infectious diseases, especially influenza and diphtheria, and as regards the latter it is well to remember Romberg's statement, namely, that even the administration of antitoxin does not necessarily prevent the occurrence of myocardial changes.

Instability of the pulse, marked pallor and vomiting, restlessness or listlessness and apathy, are symptoms which should arouse suspicion of acute myocarditis. If, in addition, the heart becomes dilated and the tones feeble, there is good reason for assuming parenchymatous degeneration of the myocardium. A soft, systolic murmur often develops which, confined to the vicinity of the apex and accompanying, but not replacing the first sound, is thought to indicate endocarditis. Such a bruit may, however, in many cases be caused by relaxation of the ventricular muscle, in consequence of which the mitral valve is not accurately closed. It is, therefore, the murmur of muscular mitral insufficiency, and in suspected cases affords corroborative testimony of the existence of some degree of myocarditis.

Interstitial, *i. e.*, suppurative myocarditis, may be suspected in the course of pyæmia or puerperal sepsis if the clinical picture resembles that of malignant endocarditis with embolic phenomena, yet without distinct signs of valvulitis. In this as well as in the parenchymatous form, however, the diagnosis will generally be by inference and can rarely be absolute. In any case it is well to remember that the probabilities are in favor of the parenchymatous rather than the interstitial variety.

Chronic Myocarditis.—The diagnosis of this affection may or may not be difficult in accordance with the extent and character of the changes in the

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heart and arteries, and the data furnished by the patient's history and symptoms. Cases may be divided into two main groups, as follows: (1) Those in which the symptoms and clinical findings leave no reasonable doubt of their real nature, and (2) those which present equivocal evidence of arterial and cardiac disease, yet are at a time of life that renders probable the existence of degenerative changes. The former group interests the physician in his capacity as a clinician and therapeutist, while the latter concerns him as a diagnostician and life insurance examiner.

1. In this division of cases, age is a very important element, since if symptoms of heart disease develop in a person who has passed the prime of life, it is a fair assumption until proved otherwise that decay of the heart muscle is responsible for his symptoms. This inference is greatly strengthened by the failure to discover, in the history or physical signs, evidence of a lesion caused by endocarditis or pericarditis. If in addition the accessible arteries are sclerotic and the urine shows the changes of chronic nephritis, or if in the absence of demonstrable changes in the vessels or kidneys, the pulse tension is abnormally and persistently high, there is good ground for believing that the myocardium has experienced a serious degree of degeneration.

If on examination of the heart the area of dulness is found increased transversely, if the first sound at the apex is valvular and feeble or impure, perhaps accompanied by a circumscribed soft murmur, and if the aortic second tone is clanging, especially if in addition at right of the sternum below the clavicle there is impaired resonance, showing dilatation of the aorta, then the chain of evidence is complete and the diagnosis of chronic myocarditis may confidently be made.

On the other hand it must not be forgotten that symptoms of cardiac inadequacy occasionally develop in persons who have scarcely turned forty and are, therefore, exceptionally young for the establishment of serious degenerative changes in the heart muscle. In such the history is an important factor, since if an acute heart strain, or a recent infection likely to occasion acute myocarditis, can be excluded it is probable that chronic degeneration underlies the incompetence. In these cases, therefore, particular attention must be paid to pulse tension and to the state of the arteries, for hypertension and stiff vessels justify the conclusion that the cardiopathy is organic, *i. e.*, a part of a degenerative process.

The history of syphilis, of the abuse of alcohol, of gout, chronic plumbism, or of other now recognized etiological factors, the discovery in the urine of albumin and casts, glycosuria, attacks of angina pectoris, nocturnal dyspnœa, or pulmonary œdema, all make strongly for chronic myocarditis, and some of them, as angina in an elderly male, leave but scant room for doubt.

2. The existence of cases of so-called latent or ingravescent degeneration or, in other words, the occasional observation of sudden death in middle-aged men who were not thought to have heart disease, makes very pertinent the query, whether chronic myocarditis can be diagnosed before symptoms declare themselves. In many cases the diagnosis must be largely inferential, and yet may be considered reasonably secure if based upon the following points:

(*a*) The history of dissipated habits or other etiological influences, such as a sedentary, often strenuous occupation in a man who in consequence of relatively too hearty feeding has developed abdominal corpulence. (*b*)

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Abnormally high blood pressure of 150 mm. Hg. or more. (*c*) Stiff or distinctly sclerotic arteries, not only the radials, but the other accessible vessels. (*d*) Urine showing changes of nephritis or glycosuria, or in the absence of albumin a deficient elimination of phosphoric acid, chlorides, etc., and often increased during the night. (*e*) An increase in the area of deep-seated cardiac dulness, especially toward the left and often of a somewhat quadrangular outline. (*f*) An aortic second tone having a peculiarly intense ringing and metallic quality. (*g*) The first sound at the apex sometimes high-pitched and valvular and seemingly of lessened intensity as compared with the second tone in the same area. (*h*) In some instances a distinct usually harsh, systolic murmur in the aortic area and occasionally after unwonted exertion, as hopping about the room, a soft, faint bruit accompanying but not replacing the first sound at the apex, and disappearing as the heart's action becomes quiet.

Unfortunately there are many cases which furnish so few or such doubtful data on which to base a diagnosis that even the most experienced clinician is puzzled to decide the question concerning the state of the heart. In such, minute attention must be paid to the history and every attempt must be made to elicit signs of myocardial incompetence. To this end the individual may be told to perform certain vigorous and unwonted physical effort, directly after which the action of the heart and its tones are to be carefully noted. If the heart muscle be not perfectly sound, it will often disclose the fact by some abnormality not previously apparent.

In particular the state of the arterial coats and the degree of pulse tension should receive careful investigation. Although the condition of the peripheral arteries is not an invariable index of that of the aorta and coronaries, still it may be held so in general. If, in addition, the blood pressure is 150 mm. Hg. or higher, or if the degree of abdominal corpulence is out of all proportion to the girth of the chest, the assumption is a fair one that the aortic coats and heart muscle are subjected to a degree of strain which is quite likely to have impaired their integrity. Should, moreover, careful examination of the heart detect a booming second tone in the aortic area or an increase of deep-seated cardiac dulness to 10 cm. or more to the left of the median line, hypertrophy of the left ventricle may be diagnosed; and hypertrophy of the heart in an individual of middle age may be regarded as synonymous with degeneration, even although the potential integrity of the myocardium may not yet have suffered appreciably.

Before closing this portion of diagnosis, it is well to say a few words concerning the recognition of myocardial incompetence in women. In them percussion of the heart is often impossible because of the mammary development, and yet there may be certain symptoms which make myocarditis highly probable. Under these circumstances valuable information may be obtained by careful palpation of the heart's impulse. It will often be perceived that the impulse is diffused and extends too far to the left, three and one-half to four or more inches instead of three or less from the median line. Upon auscultation the first sound at the apex is not clear and strong, but valvular, or actually impure, and the aortic second is accented. In other instances it is the pulmonic second that is intensified. If in addition the pulse tension is too high, and the woman suffers from greater breathlessness on exertion than should be the case in relation to weight or anæmia, and if she be leading a strenuous social, domestic, or club life, the assumption is tolerably safe of a

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chronic myocardial weakness, and if the age be fifty or thereabouts this weakness probably rests upon a basis of chronic myocarditis.

The Fatty Heart.—The existence of fatty overgrowth and infiltration to an extent occasioning myocardial incapacity must be a matter of inference rather than clinical demonstration. In the majority of fat persons who present cardiac symptoms the most we can do is to diagnose the incompetence. If the individual is very fat and at the same time anæmic, is too young to warrant the assumption of cardiovascular and renal degeneration, and accordingly fails to furnish clinical proof of such degenerative changes, we may recognize heart strain as probable without degeneration. The case may then be said to come within the category of the myocardial incompetence of the obese. As a matter of practical interest it is not necessary to know whether the heart is actually fatty or not; it is overpowered by the general obesity, and this of itself forms a sufficiently serious condition.

Prognosis.—This is necessarily grave, since whatever impairs the structural integrity of the heart muscle is likely to limit its potential capacity. The heart is, however, a marvellous organ, whose possibilities for compensatory adjustment to altered conditions enables it to perform its function in a way that is truly astonishing. Accordingly it may be performing its work with but slight evidence of anything being wrong, while all the time a process of degeneration is going on that is surely but slowly undermining its resistance.

Acute parenchymatous myocarditis may be recovered from, when not extensive, but the possibility of sudden death should always be borne in mind, especially during the course of diphtheria and even after convalescence. On this account a child should be kept under close observation, both when at play and at rest, for the detection of slight signs of incompetence. The *interstitial form* of acute myocarditis is probably always fatal, unless it be very circumscribed, which is not usual.

Chronic myocarditis also carries with it the liability to sudden and unexpected death, and since we possess no means of determining the seat of dangerous lesions, we must always regard as uncertain the life prospect in any individual with myocardial degeneration. Nevertheless, if hypertrophy predominates and symptoms of inadequacy cannot be discovered, we may hope that the potential integrity is still such as will preserve the heart from incompetence so long as it is not too greatly overtaxed. When, however, signs of incompetence once appear, prognosis becomes very serious and must be reckoned by the degree of insufficiency manifested, or by the response shown to proper treatment.

Persistent arhythmia is generally held to be of worse import than is regularity even with tachycardia when this latter is not extreme. However, one should look with apprehension on habitually accelerated and regular pulse, whereas irregular hearts may endure for years without serious incompetence. Degeneration of the left ventricle is more serious than degeneration of the auricles, and it is in the latter condition that arhythmia is so common; while, according to Hampeln, extensive fatty change in the wall of the ventricle is compatible with perfect regularity of action.

Angina pectoris is of evil prognosis, since, in the majority of cases, there is more or less interference with coronary circulation, and this condition always carries with it the possibility of sudden death. The prognosis in cases of myocardial incompetence, associated with chronic nephritis, is likewise

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very bad. The heart muscle may be assisted in doing its work for a time after the initial manifestations of its weakness, but when the break again occurs the mischief is likely to be irreparable. The development of the gallop rhythm always, in the writer's experience, has portended a not very remote termination in death. This rhythm of the sounds may persist for months, but it indicates a degree of strain of the ventricular wall to which it must inevitably yield in time.

It should be remembered that a heart weakened by chronic myocarditis may be capable of performing its functions, fairly well, so long as some extra burden is not imposed. Any illness, however insignificant it may seem to be at first sight, may prove the last straw. This is particularly true of acute infections, as influenza.

Fatty heart, or the cardiac incompetence of the obese, is extremely serious and is rarely recovered from when it has become pronounced. The more corpulent the individual the worse the prognosis, since it is hardly likely that the obesity can be materially reduced without endangering the nutrition of the heart muscle. In elderly and fat persons there is probably chronic myocarditis, as well as general obesity, a combination which is practically hopeless.

Treatment.—Preventive.—It is not to be inferred that we possess the power of wholly preventing the various changes in the heart muscle that have been considered; but there can be very little doubt that, if physicians were fully alive to the injurious effects resulting from the conditions of modern life, they could exert appreciable influence over those patients whose habits or constitutional tendencies are fraught with danger. This remark applies, of course, to chronic myocardial disorders, since acute myocarditis is only preventable in so far as are the acute infections.

There is an aspect of this matter of prophylaxis which even, as regards acute parenchymatous degeneration, falls within the limits of professional possibility. This is the prevention of heart strain, which is oftentimes the factor that induces myocardial incompetence. Efforts in this direction must be both educational and therapeutic. "What," the writer was once asked, "are we to do to preserve the heart of the elderly man whom we find has signs of myocardial weakness?" The reply first suggesting itself is, inform him of his danger if he subjects his heart to avoidable strain. He should be told not to run for trains, not to climb mountains, not to commit excesses in baccho et venere, not to overeat, not to smoke strong Havana cigars to excess, in a word, not to do those many things which are likely either to dilate the heart acutely or to tax habitually its limited powers of endurance.

If a man is leading a too strenuous business life, he must be warned of the positive danger lurking in its continuance. If a woman is devoting herself too strenuously to social functions, charitable or club work, etc., she must be told to limit them and take life more easily henceforth. If the physician will take the trouble to inquire minutely into the history of a patient, for weeks or months immediately prior to the initiation of his symptoms, he will be surprised to learn how often there has been some unusual business, social, domestic, emotional, or recreational strain as the real determining cause of the myocardial breakdown. In not a few instances this is found in an arduous day's tramp in the mountains, in close confinement to business without a vacation, in prolonged worry over financial or domestic difficulties, etc. Therefore, the physician must make good advice paramount to pre-

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scriptions, in the case of persons whose hearts are believed to be no longer sound.

High-pulse tension must be lowered if possible, or at least kept from becoming still higher by restriction of the dietary, by cathartics, and, in women, by regulation of the clothing when this is too tight. Not only is the food to be restricted to an amount the caloric value of which is not excessive, but articles must be cut out which lead to intestinal fermentation. Flesh foods in particular must be taken moderately, and strong stock soups and broths must be forbidden on account of their extractives, which stimulate heart action unnecessarily. Fried dishes are injurious because of the fatty acids they contain, and must be interdicted.

The daily drinking of immoderate quantities of water increases the labor of the heart, and should be stopped. Strong coffee and tea also tend to endanger the integrity of the myocardium by exciting the heart, and whatever puts unnecessary work upon it tends to its ultimate enfeeblement. For this reason alcohol is bad for these patients and should be forbidden. The smoking of strong Havana cigars often accelerates the heart and is said to augment blood pressure, and therefore to be injurious from a preventive as well as a therapeutic standpoint. They must be forbidden altogether, greatly reduced, or replaced by mild, domestic cigars.

The occasional use of a mercurial and saline cathartic is very beneficial in this class of cases. Many of these persons declare they do not require such remedies, because they are and always have been perfectly regular in the matter of a daily stool. The cathartic is not ordered because of constipation, but because most of the patients who have high-pulse tension show abdominal corpulence, or a marked tendency thereto, and, being hearty feeders, generate injurious toxins in their intestinal tract. For such individuals, therefore, it is highly beneficial to order a thorough removal of these toxins by a brisk cathartic. This is particularly advisable the morning after a banquet or dinner party. It is often truly remarkable how much better these people with high tension breathe and appear, after such a cleaning out of their colon. In some instances the blood pressure falls appreciably after a calomel and saline purge.

Tight clothing about the abdomen is a serious menace to women with high tension, since whatever occasions pressure upon the abdomen tends to raise blood pressure through the action on the splanchnics. It is on this account that deep massage of the abdomen is especially harmful to patients with chronic myocarditis. Gentle massage may be grateful to persons suffering from flatulent distention, but too deep manipulation of the abdominal walls may seriously embarrass the breathing.

Medical gymnastics form another measure of the very greatest utility in the preservative management. They are especially serviceable for persons who are obese or have an excess of abdominal fat. Such individuals are apt to sit for hours together at their desks, and the heart on this account being deprived of the aid to circulation furnished by muscular exercise and deepened respiration, is obliged to drive the blood onward against the impediment occasioned by the distention of the intra-abdominal veins.

The most beneficial exercises are not the so-called resistance exercises, but breathing exercises and other light gymnastics, all performed with the assistance of some person who is trained to this work and can be trusted not to carry the various movements to the point of causing embarrassment to the

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respiration and circulation. More than one man, who was beginning to evince symptoms that threatened before long to merge into pronounced myocardial incompetence, by means of such exercises, carried out for a number of weeks, has been restored to a condition of such comfort that he considered himself entirely well.

Self-resisting exercises, which may be excellent for persons with sound hearts, are attended with the possibility of harm; so also is the use of certain mechanical devices for exercise, since in his enthusiasm the individual with high-pulse tension, or an already hypertrophied heart, is likely to put himself seriously out of breath and embarrass his heart.

The purpose of these exercises is to ease the work of the heart, and whenever they cause palpitation or actual dyspnœa, the myocardium is being overtaxed, not lightened of its labors. Golf is an excellent form of exercise for this class of patients, provided it is not played too violently or for too long a time. Walking is also beneficial, but like golf must not be continued to the production of much weariness and must not be at a pace that induces shortness of breath and palpitation. Oertel's hill-climbing or "terrain kur" is likewise good when carefully supervised by a physician. In fact, almost any form of muscular exercise may be made beneficial which promotes easier breathing and a more active circulation without great fatigue. *Per contra*, whatever produces dyspnœa, palpitation, or a sense of fulness and discomfort in the precordium is fraught with danger to persons who show portentous elevation of blood pressure or breathlessness.

Medicinal agents play a minor role in the prevention of myocardial incompetence. When arterial hypertension is a marked feature, it may be necessary to prescribe remedies which exert a vasodilator action, in the hope of lessening vascular resistance. Nitroglycerin, sodium nitrite, erythrol tetranitrate are the drugs most commonly employed. The action of nitroglycerin is rapid and too evanescent to be of much real service. Nitrite of sodium is less transient in its action and may be given in doses of 1½ to 2 grains without producing the headache so commonly experienced after nitroglycerin. Erythrol tetranitrate is said to exert a still more sustained effect than the remedy just mentioned. It may be given in doses of ½ grain every three or four hours. Even as regards these two remedies, candor compels one to express the same skepticism concerning their ability to materially reduce pulse tension, unless their action is reinforced by other measures tending to the same effect.

Palpitation is quite commonly experienced by persons having high-pulse tension, especially upon some physical effort not great in itself. This symptom, as well as the slight breathlessness that may accompany it, can often be controlled by the conjoined use of sodium nitrite and tincture of aconite. These remedies should be taken several times daily and not merely at the time of the palpitation. The dosage required will vary, but in general 1 grain (0.06 gm.) of the sodium salt and 5 minims (0.3 cc.) of the aconite (U. S. P. 8) will prove sufficient. One may not hesitate to prescribe the aconite in much larger amounts, up to 10 or even 15 minims, provided its effect be watched. This medicine is infinitely preferable to digitalis, which, when tension is very high, is quite likely to intensify rather than lessen the troublesome palpitation.

Cathartics have already been mentioned. Not only is their beneficial effect to be attributed to their hydragogue action, but they prove most bene-

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ficent by washing out toxic substances from the intestinal tract. In a similar direction is the often highly beneficial effect seen to follow the use of antiseptic remedies, as sulphocarbolate of zinc, inspissated and purified ox-gall and various other preparations. They tend to lessen arterial tension by preventing flatus.

Management in the Stage of Incompetence.—The character of the changes in the heart and their association with degenerative lesions in the blood-vessels and kidneys preclude all thought of restoring the heart to a condition of health. The most that can be hoped for is an improvement in its working capacity. Some patients respond to treatment in a truly remarkable manner, while others appear to possess no recuperative power at all. In the former class all that seems necessary is to ease up the work of the organ by rest, to reduce congestions by cathartics, and to give the heart a lift, as it were, by some cardiac tonic, and the machinery of life goes on again nearly the same as before.

In the second class of cases it soon becomes apparent that the mechanism is bound to run down in spite of all efforts to arrest its decline. Unfortunately these form the majority, and consequently the treatment of myocardial incompetence may be pronounced most unsatisfactory. This is emphatically true of the nephritis cases. In them the hypertension is so great as to prove an insurmountable barrier to restoration of heart power. Whatever improvement may be gained in the beginning is soon lost and rarely if ever returns. Before long the hypertension is succeeded by hypotension, and when this latter comes on the doom of the patient is sealed.

Rest.—We possess no measures for the treatment of myocardial insufficiency which are different from those applicable to the broken compensation of valvular disease. There are certain conditions, however, depending upon the degenerative changes in the heart and other organs which compel us to modify somewhat the application of these measures. Foremost among the limited means at our command is the enforcement of physical rest. It goes without saying that if the heart is unequal to the demands made upon it, these demands must be lessened. Accordingly, if an individual suffers from dyspnœa on effort, he must not make the effort but must rest his body in order to give his weakened heart a rest. The rigor with which this injunction is enforced must be determined by the degree of incompetence. In some cases this must be absolute in bed, while in others it may be necessary only to confine the patient to his room or to his bed, with permission to walk to the toilet when near by and on the same floor. In early cases, showing only or chiefly breathlessness on exertion, this amount of rest, reinforced by other measures to be mentioned, may be sufficient to restore the individual for a time.

If the left ventricle is greatly dilated and feeble, a condition which, under the strain of physical exertion, predisposes to sudden diastolic arrest, rest in bed should be absolute. In some of these cases paroxysms of dyspnœa (smothering spells) are so distressing that patients declare they cannot remain in bed. For such, as will be detailed later on, it is often well to allay the subjective sense of dyspnœa and to produce quiet of mind as well as of body by the hypodermic administration of morphine. In this way, one rarely fails to secure necessary repose.

Although absolute rest is essential *at first*, still it is not well to continue it for too long a time, especially if the heart has profited appreciably by the

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measure. The heart is the central organ of circulation on which the main work depends, but nature never intended this organ to carry on the flow of blood unaided. Various auxiliary factors are to be found in the elasticity of the vascular coats, in muscular contractions, and in respiratory movements. If now an individual with stiff arteries is compelled to lie perfectly still in bed for days together the factors of muscular action and respiration are largely abolished and the work of maintaining the blood flow falls more heavily on the weakened left ventricle than it can bear, and in time the benefit expected from rest in bed is counteracted.

Because of the considerations just mentioned, it has long been the writer's practice, in cases of serious myocardial inadequacy, to supplement enforced rest from active, voluntary movement by resistance exercises and massage, as will be again considered. It always seems well for these patients, who are allowed to break their rest by going to the toilet, sitting up, etc., to understand the strain put upon the weakened heart muscle by sudden assumption of the erect posture. Therefore, it is well to explain to them the injurious effect of rising quickly from the recumbent posture to the feet, since a damaged heart cannot always adjust itself promptly to the sudden muscular contraction thereby occasioned. The sudden increase of intraventricular blood pressure thus produced subjects the left ventricle to instantaneous strain. It is inability to withstand the dilating force of such an action which causes so many of these patients to die directly after having arisen to their feet. Accordingly, they should be told to make such changes of attitude slowly and cautiously.

Resistance Exercises.—As previously stated, absolute rest in bed for a long time imposes upon the heart the task of maintaining the blood flow without the help of those accessory factors found in muscular contraction and vigorous play of the diaphragm, and other respiratory muscles. Therefore, in all cases of myocardial incompetence the heart should be assisted by properly conducted exercises, *i. e.*, resistance exercises. Space does not permit a discussion of their modus operandi, or a description of the method of their administration. These may be found in special treatises and in numerous papers that have appeared in medical journals.

It must suffice here to state, that although, as shown by their name, they consist of certain movements on the part of the patient made against resistance offered by a skilled operator, still they must be executed with such gentleness and precision as not to impose any additional burden upon the weakened myocardium. If the degree of resistance is properly applied to the patient's condition, the movements lighten the labor of the heart.

When the myocardium is very feeble it is well to have the exercises made while the patient remains lying in bed. As his heart improves he may sit up during his resisted movements, while only after considerable gain in the strength of the heart has been made are the daily treatments to be taken in the standing position. In the same cautious manner are the exercises to be increased in number and duration.

The precise mode of action of these resisted movements is not perhaps fully understood. They serve, however, to divert the blood from the heart to the extremities and thus to reduce its dilatation. Whether they can do all that is claimed for them by some, they certainly are serviceable to this class of patients by affording them a beneficial rather than harmful mode of offsetting possibly injurious effects of rigid rest in bed. Their effect upon

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metabolism has not been carefully studied, but, theoretically, they should prove of great benefit in this direction to individuals deprived of active bodily exercise.

Massage.—This is another excellent means of counteracting the harmful results of prolonged recumbency by promoting the return flow of the blood. The caution should always be imposed, however, of not having the abdomen massaged deeply and strongly, since this raises blood pressure and may prove injurious.

Nauheim Baths.—The ever-increasing stream of patients to Bad-Nauheim, Germany, attests the popularity and efficacy of the baths there given for the treatment of heart disease. In no class of cases is this form of hydrotherapy more beneficial than in those of chronic myocardial incompetence. As with other therapeutic agents this should not be left for a last resort, but should be instituted early before marked dilatation has set in. The degree of improvement, objective as well as subjective, is often truly surprising. Since the tendency in these cases is for signs of incompetence to re-assert themselves, after the patients have returned to their accustomed mode of life, people of means should be advised to make the journey to Bad-Nauheim every summer.

There are a number of reasons that may make it necessary for the physician to treat his patient at home instead of sending him to Germany. Among them is the fact that the health resort in question is only open from the first of May to the early part of October. Accordingly, it is recommended that when the baths cannot be had at Bad-Nauheim, they should be given in the home or elsewhere by means of artificially prepared waters.

So many articles have appeared describing these waters and the mode of their administration that no attempt will be made to do so here. Caution may well be urged, however, against the employment of such baths without careful study of their indications and mode of action, so far as this is understood. The manufacturers of the so-called effervescing bath tablets send out circulars which make it appear that this form of therapy is very easy and simple in its application, and that from the start the baths should be charged with carbonic acid. They say common salt or sea salt may be added to the bath, but is not essential. Now such statements are misleading and likely to do harm, since, as is well known, it is not customary at Bad-Nauheim to begin a course of treatments with carbonated waters.

Very feeble, dilated hearts do not require and will not endure stimulating baths, but need soothing, slightly tonic baths. Therefore, it is always well to begin with warm, saline, but not effervescing waters, and to come to the use of carbonated baths very gradually and only when the temperature of the water is such as to make it stimulating, and when the heart has gained sufficient strength to enable it to respond to such energetic stimulation as results from cool, strongly saline and effervescing waters. Hence it is plain that unless care and judgment are exercised, this form of therapy may become injurious instead of beneficial.

Digitalis.—So great is the dependence upon this remedy in cardiac disease, that most practitioners prescribe it at once, so soon as they recognize signs of myocardial insufficiency. In the class of cases now considered, the selection of a heart tonic should be largely determined by the degree of arterial tension and the state of the vascular coats. If the blood pressure is high or the vessels are stiff, digitalis must be administered with great

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care. If this caution is not observed it will frequently be found that dyspnœa and palpitation are augmented rather than decreased. This is particularly the case in the myocardial inadequacy following upon chronic nephritis. *Strophanthus* may be preferable in cases showing hypertension, and yet even this remedy is not always well tolerated or efficient. Whenever, therefore, these drugs do not relieve symptoms they should not be persevered with in increasing dosage, but must be replaced by others soon to be mentioned, or must be associated with a vasodilator.

Tincture of Aconite.—Although this remedy is a heart poison, experience has convinced the writer of its great utility in some cases. These appear to be such as manifest annoying palpitation and irregularity of heart action, especially under the use of digitalis and the like. 5 to 10 minims (0.3 to 0.6 cc.) of the tincture of aconite root (U. S. P. 8) may be taken three or four times daily with very great benefit in many cases. The remedy does not appear to relieve dyspnœa so much as excited heart action, which is not an indication of strength but of weakness, and hence is a wasteful expenditure of energy.

Vasodilators.—These are sometimes highly serviceable in cases showing hypertension. As previously stated but little effect can be demonstrated from these agents upon pulse tension, and yet in conjunction with digitalis, strophanthus, and especially aconite they may afford marked relief. A combination which frequently gives decided benefit to the dyspnœa, as well as palpitation, is nitrite of soda, tincture of aconite, and tincture of strophanthus. The exact dose of each remedy cannot be laid down, but must vary in accordance with the degree of tension and the signs of myocardial incompetence exhibited in each case.

Sparteine Sulphate.—This remedy, much vaunted by the French, is of service when there is marked arhythmia and the auricles are dilated. It will fail strikingly in some instances and prove highly efficient in others. Why this is cannot be satisfactorily explained. In a patient recently under observation, digitalis, even when cautiously administered, seemed only to augment the dilatation and arhythmia, whereas sparteine, in moderate doses, exerted an opposite effect. The remedy may be ordered in doses from ½ to 1 grain (0.008 to 0.06 gm.) alone or in combination with others.

Ammonia.—There are patients who do not bear drugs that slow the pulse and contract the vessels. Some of these show a tendency to bradycardia, while others do not, but manifest feebleness of the left ventricle. It would seem as if the heart needs stimulation and quickening in these cases rather than slowing, as if it were not able to handle the increased amount of blood entering it during its prolonged diastoles At all events the aromatic spirit of ammonia, in 15 minim (1 cc.) doses every two or three hours, has produced a striking improvement.

Caffeine and Strychnine.—These are excellent remedies with which to sustain flagging hearts, when digitalis and strophanthus are not admissible. They are both given best by hypodermic injections, the former in doses of ½ to 1 grain (0.03 to 0.06 gm.) several times a day, and strychnine in doses of $\frac{1}{60}$ grain (0.001 gm.) at three or four hour intervals. Large doses of strychnine are to be deprecated, rather than recommended, as likely to produce short and ineffective systoles.

Diuretin.—This is a powerful diuretic for patients displaying marked and ever-recurring œdema. It may be given alone or in combination with

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digitalis infusion, preferably alone and in solution. The objectionable taste can be disguised by essence of pepsin. The daily dosage may be from 60 to 120 grains (4 to 8 gm.). Diuretin may be administered at intervals over a period of many weeks or months, and will do much to prolong life even when restoration to health is impossible.

Cathartics.—These may be mentioned in connection with diuretin, since they also prove a powerful means of removing œdema. To this end they should be as unirritating as possible, and must be given in such amounts as will produce many copious watery stools every day or every other day. One great reason why physicians fail to secure the effect desired over the dropsy and the hepatic stasis lies in their failure to recognize the clinical fact that, since transudation of serum is constant, its removal by means of hydragogue cathartics should be accomplished daily and not occasionally. Sulphate of magnesia in saturated solution and elaterine are the most efficient remedies of this class. The former is disagreeable to taste but is not drastic; ½ ounce in 1 ounce of water may be taken hourly until the desired result is obtained. Elaterine is apt to excite emesis, but will certainly cause the evacuation of large amounts of fluid when calomel and other cathartic remedies fail.

Of course the repeated and prolonged use of remedies calculated to remove dropsy will in time be followed by emaciation and anæmia, in consequence, partly, of the daily loss of important salts contained in the serous transudate and the copious, fluid stools. Deplorable as this is, it cannot be avoided. It is a question of allowing the patient to die from stasis, or to prolong life at the expense of inanition and hydræmia. Consequently when the system is being drained by these diuretic and cathartic drugs, the effects upon nutrition must be offset so far as possible by simple, nourishing food, iron, arsenic, etc.

Another reason for the exhibition of cathartics, at least early in the fight against myocardial incompetence, lies in their ability to lessen hypertension. It is often surprising to witness the relief from dyspnœa and pain experienced after a sharp purge. When this alone is the effect desired, a mercurial followed by a saline is the best, and it does not require frequent repetition. This must be governed by the degree of tension and the character of the symptoms. On the other hand, constipation should never be permitted, since it raises the tension of the pulse and induces injurious straining at stool. A moderate amount of saline daily and a sharp calomel purge, occasionally, is advisable in most cases.

Morphine and Heroin.—There is no single remedy of more signal benefit than either of these two therapeutic agents when properly used. If a patient with myocardial incompetence is suffering from smothering attacks which rob him of sleep and compel him to sit up the greater part of the night, surprising relief is usually afforded by a hypodermic injection of a small dose of morphine; ⅛ grain is better than ¼ grain, since it will stimulate the heart and prevent the dyspnœa. In most instances it also induces refreshing sleep. The effect of the morphine is enhanced by the addition of $\frac{1}{200}$ grain of atropine. If a saline cathartic is administered every morning, no unpleasant gastric effects are experienced, and the morphine may be injected in the same dose for a period of days or even weeks without harm. In some patients morphine does not allay the attacks of nocturnal dyspnœa, and heroin may be tried; $\frac{1}{12}$ grain (0.005 gm.) can be given hypodermically at night.

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It not infrequently happens that the physician is called to treat one of these sufferers after the stage of profound inadequacy has been reached. The heart is greatly dilated and arhythmic, the legs are œdematous, the liver and lungs are congested, and the patient is unable to lie down because of attacks of suffocation which make him spring up and sit on the edge of the bed. Under such conditions digitalis is really worse than useless; besides, it has probably been tried and found wanting. The plan of management, which has proved most efficient is a dose of morphine at bedtime, a sharp purge by elaterine or salts to lessen stasis in the lungs and abdomen; $\frac{1}{60}$ grain of strychnine and 1 grain of caffeine, each hypodermically four times a day, and milk diet for twenty-four to forty-eight hours according to circumstances.

By a sharp purge is meant not two or three fluid stools of six to eight ounces each, but a dozen profuse washing passages which remove several quarts of water. Then for several successive days the bowels are kept freely open, until the abdomen is soft and the liver no longer tender. When it is found that the heart has become reduced in size, slower and stronger in action, a careful trial of digitalis is made. In a word, the initial object is the reduction of venous stasis by depletion and not by trying to spur up the already overtaxed heart. This latter will not and cannot respond until after it has been relieved of some of its load and has rested somewhat.

Venesection.—Undoubtedly there are many cases in which the letting of 20 to 30 ounces of blood proves a very timely measure and starts the patient on his uphill journey. When arterial tension is so high and the pulse so bounding as to congest the head and threaten apoplexy, a vein may be opened and 16 to 20 ounces of blood be abstracted with immense benefit. Nature sometimes gives a hint in this direction by the production of severe epistaxis. The nose-bleed is sometimes very hard to arrest and requires plugging of the nares, but afterward the patient is unquestionably relieved from a condition of hypertension which might have proven most dangerous.

Nourishment.—The heart being an organ that is required to perform almost incessant work, must receive adequate nourishment if it is not to suffer in its integrity. Nevertheless, the digestive disturbances resulting from circulatory embarrassment, often occasion so much discomfort, if not actual repugnance for or positive inability to consume food, that the nourishment of the individual and the selection of food become matters of great difficulty. It is generally held that the dietary should be rich in proteids, and within certain limits such is undoubtedly the case. Moreover, articles of animal origin are likely to be digested with less distress from gas than are cereals and vegetables rich in carbohydrates. But whatever be the form of food selected, it should not be in large amounts lest distention of the stomach and increase of dyspnœa be occasioned.

Digestion is apt to be slow and absorption less rapid than in healthy persons without hepatic and gastric stasis. Consequently, it is a good rule not to administer food at very short intervals. Likewise the intake of fluids should be restricted, especially when there is dropsy and attempts at its removal are being made. Milk may be very serviceable in some cases, and it may be wise to confine patients with abnormal pulse-tension to an exclusive milk diet for a few days until the pressure has been reduced. Coffee and tea should be allowed, but sparingly. In some cases, particularly if the individual has been accustomed to wine or strong beverages, it is a good

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plan to allow a small quantity of such liquids. They not only improve appetite and digestion, but serve as positive nourishment to weak hearts when taken in limited amounts, and particularly with meals.

NEW-GROWTHS AND PARASITES IN THE MYOCARDIUM.

1. **Syphilis.—Etiology.**—Cardiac syphilis is a late manifestation of the infection, not appearing until five or ten years after the initial sore. It is not confined to either sex or to any age, but is said to have been discovered rather more often in the male sex. Its occurrence by preference in adults is accounted for by its being the result of acquired rather than congenital syphilis.

Morbid Anatomy.—This disease may give rise to changes of a chronic nature in any of the cardiac structures, but the endocardium is the least likely to be affected. In the heart wall the disease appears either as a sclerotic process or as gummata, which changes may be associated with fibrous thickening of the endocardium or pericardium. Of the two forms in which myocardial syphilis may occur, the sclerotic is by far the more frequent. It affects chiefly the wall of the left ventricle and appears as circumscribed patches of fibrosis. According to Loomis, this fibroid transformation may be diffuse, but Runeberg holds that its occurrence in limited areas is characteristic.

The coronary arteries generally display the changes of obliterative endarteritis, that is, cellular infiltration and thickening of the subendothelial layers and consequent obliteration of the lumen. Osler states that gummatous peri-arteritis may affect the coronaries as well as the arteries of the brain, although less frequently. This is the only form of arteritis which can be regarded as specific. Should the endarteritis obliterans of Heubner be found in association with syphilitic lesions in other parts of the heart, or other organs, its luetic nature may be regarded as assured.

Gummata in the heart wall are comparatively rare, and yet numerous instances have been reported since Ricord's case, in 1845, first called attention to the possibility of such an occurrence. The tumors may be recent, or old and single or multiple; the gumma appears as a soft, grayish mass of variable size surrounded by a capsule of fibrous tissue. Old gummata are dry, caseous, and yellowish white. The pericardium overlying the gumma is usually seen to be thickened but seldom adherent. There may also be outgrowths upon the valves, as reported by Janeway and others, in association with gummata in the myocardium.

Symptoms.—Heart syphilis is far less often recognized clinically than postmortem. The explanation lies in the fact that it is quite apt to remain entirely latent and to be first declared by the sudden death of the patient. Even when symptoms are produced, they do not present features that may be considered characteristic or distinctive. *Tachycardia* and *arhythmia* have been emphasized by Semmola. They may occur alone or together, but to be significant of the disease in question must be independent of any other discoverable cause, as dilatation or valvular disease. In a case reported by Ashton, Norris and Lavenson, there was bradycardia with convulsive seizures and other features of the Stokes-Adams syndrome; after death from heart block, a gumma was found in the intraventricular

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septum involving the bundle of His. *Precordial* pain of an indescribable or dull character, or of the nature of a vague distress rather than actual pain, has likewise been described. *Angina pectoris* also has been noted, and when occurring in a person under forty-five years of age, is very suspicious of coronary sclerosis due to syphilis, and would warrant a resort to mercury and iodides.

Examination of the heart may or may not reveal signs of disease. There may be appreciable enlargement of the organ, or on careful percussion its area of dulness may appear entirely normal. This latter is one of the points on which Runeberg lays stress in connection with suspicious symptoms. Not infrequently the tones are clear and present no departure from health, but Runeberg has observed a muffling or tonelessness of the first sound at the apex. Should the valves be sclerotic, there may be murmurs or abnormalities corresponding with the nature of the valvular changes.

Diagnosis.—Except in unusually fortunate cases this must be inferential or problematical. The occurrence of some of the symptoms mentioned in an individual furnishing evidence of syphilis in other parts would render the diagnosis reasonably certain. The existence of cardiac lues would be a fair assumption, if an individual with an undoubted history of a chancre, five or more years earlier which had been insufficiently treated, should present evidence of cardiac disease for which no other satisfactory explanation could be discovered. In most cases, therefore, the diagnosis must be established by exclusion rather than direct evidence. Tachycardia and arhythmia, without obvious signs of disease in heart or bloodvessels, and to account for which no disturbing factors can be discovered in other organs, is, according to Semmola, good and sufficient ground for a trial of antisyphilitic medication. The development of angina pectoris in a man under forty-five may also be considered of luetic origin, provided no other satisfactory cause can be determined.

Prognosis.—This may be said to be good, provided treatment is instituted before the development of irremovable changes. When unrecognized and, therefore, untreated, this form of myocardial disease is likely to lead to a fatal termination in the course of time. Extensive coronary sclerosis is very likely to terminate in sudden and unexpected death. Accordingly, the development of anginal seizures of this origin possesses a very grave significance and renders the individual wholly uncertain of his life.

Treatment.—This must of course be antisyphilitic, in the hope of arresting or removing the changes. To be efficient, the remedies should be pushed to the limit of toleration and ought to be continued for some time after the cessation of symptoms. Other therapeutic measures in addition may be necessary, for the purpose of meeting such symptoms as may arise. In particular the heart should be spared from strain during the course of specific treatment and the individual's general health receive close attention.

2. **Tuberculosis.**—**Etiology.**—Tubercles occur in the myocardium in connection with tuberculous pericarditis and in general miliary tuberculosis.

Morbid Anatomy.—This requires very limited consideration in this place, since it possesses greater pathological than clinical interest. The disease may be discovered as miliary nodules scattered through the myocardium, as caseous masses or as a diffuse sclerotic process. The tubercles are said to be discovered especially in the sulci along the line of the vessels. Caseous tubercles are exceedingly rare, while the sclerosis of tuberculous origin

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presents no features that distinguish it from the same process of other causation.

Symptoms.—If such are produced they are obscured by those of the tuberculous infection in general. The invasion of the heart is said to occur chiefly in acute cases, and hence any rapidity or feebleness of the heart's action that may be observed is likely to be attributed to the asthenia and pyrexia of the primary affection.

Diagnosis.—This can be made with certainty only in the postmortem-room. Its clinical recognition can have no practical bearing on the management of the case, and hence proves of interest only as an instance of the refinement of *intra vitam* diagnosis.

Prognosis.—This is in reality that of the primary infection. It probably exerts but little influence on the course of the malady.

Treatment.—Treatment is that of the disease in general and includes the administration of digitalis, etc., if cardiac asthenia becomes pronounced.

3. **Blastomycosis.**—Another of the rarities of medicine is the dissemination of blastomycotic granules in the myocardium. They occur as a part of generalized blastomycosis, of which some seven undoubted instances have been reported. In the case recorded by Cleary[1] the fungi were discovered in the myocardium as an accidental finding of the postmortem. The heart weighed 180 grams and scattered through the heart walls were miliary nodules resembling those of tuberculosis. On microscopic inspection they were seen to be made up of aggregations of polymorphonuclear and mononuclear leukocytes; while giant cells were seen enclosing the characteristic fungi. These nodules exhibited a slight tendency to central necrosis. They were not surrounded by a limiting inflammatory zone. The muscle fibers were rather narrow and displayed a slight polar pigmentation. The middle coats of the smaller arteries appeared homogeneous, as if having suffered amyloid degeneration.

The clinical picture in this case was that of chronic nephritis. The patient was an Italian, aged twenty-three years, from whom no clear anamnesis could be obtained. On admission to Cook County Hospital, in May, 1903, he was very weak and had a cough. The pulse was rapid and feeble and so remained until death, nine days after his entrance. The lower extremities were slightly œdematous, and the scanty urine contained abundant albumin, and hyaline and granular casts. The right lung showed slight dulness and exaggerated breath and voice sounds over the upper lobes. Fever was not present.

From the foregoing it is plain that blastomycosis of the heart possesses no clinical interest, since it is secondary and but a part of the generalized disease, and can only be surmised, not diagnosed, during life. It is doubtful if it materially influences the prognosis of the case which, to judge from reports, is absolutely hopeless.

4. **Actinomycosis.**—It will probably surprise the reader to learn that actinomycosis of the myocardium is more frequent than is either syphilis or tuberculosis in this situation. Such at all events is the statement made by Hektoen, in an unpublished paper to which he has kindly granted access. As the disease commonly invades tissues by direct extension, no anatomical structures in the body are exempt from its inroads. Accordingly, any portion

[1] *Transactions of the Chicago Pathological Society*, 1904, vol. vi.

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of the circulatory system may be attacked, but the endocardium would appear involved rather less frequently than is the pericardium or heart wall, and then in consequence of encroachment of a myocardial process upon the cavities of the organ.

Etiology.—The invasion of the heart may be either by direct extension from surrounding structures, or by way of the blood stream. Involvement through the lymphatics has not yet been demonstrated. The metastatic form is stated to be the more common, which is not surprising when one understands the frequency with which actinomycotic masses are found projecting into the interior of the veins in various parts. When the process has extended from the lungs or other adjacent structures, there are generally dense fibrous adhesions binding together the various tissues.

Morbid Anatomy.—Actinomycotic granules within the myocardium vary much in number and size. They have been found in all portions, including the auricles and papillary muscles. These foci are more often metastatic in origin and hence may be either single or multiple. Their size is also not constant, but the majority range between 1 and 4 cm. in the greatest diameter.

The largest mass on record is that of Ponfick, which was a yellowish nodular mass, of the size of an apple, situated in the wall of the right heart at the level of the auriculo-ventricular opening. Its projection into this ostium materially narrowed its lumen, while two of the tricuspid leaflets, the posterior and a large portion of the middle, were lost in the mass. The endocardium over this growth was smooth; but such is not always the case, since in the instance described by Paltauf of a nodule, 3 by 1.5 cm., located in the wall of the right ventricle, small, subendocardial masses depended into the cavity of the ventricle and over these the endocardium presented superficial ulcerations. At first glance the large mass found by Ponfick resembled a sarcoma or gumma, but on being divided the cut surface showed many miliary yellowish foci which contained sulphur-colored granules of actinomycosis. This mass was connected by coarse bands of granulation tissue, with an extensive actinomycotic fibrous proliferative and suppurative process which filled the right half of the pericardium.

In another instance Ponfick observed that the larger nodules were composed of smaller granules, which were partly distinct and partly coalescing, each of which presented an outer, grayish-pink, rather firm stratum, and an inner zone or centre of softening. In a nodule described by Abbée, and situated in the wall of the right ventricle, the section showed a yellowish-white surface with foci of a greenish-yellow color. This appearance was found due to the mass being made up of a coarse, fibrous tissue, enclosing spaces or meshes which were filled with pus and actinomycotic granules. At the periphery the cells of the heart muscle were pale, swollen, granular, and had lost their striations, the nuclei becoming more and more vesicular as the sarcoplasm underwent disintegration.

Foci of myocardial actinomycosis are very apt to set up either circumscribed or diffuse pericarditis, which may be exudative or fibrous. The exudate may be fibrinous or serofibrinous, and in some instances purulent. Not infrequently this exudate is found to contain the characteristic sulphur granules of the actinomycotic fungi. In one instance, described by Munch, the base of the heart was united by firm adhesions to the right lower lobe; there was pericardial actinomycosis, and actinomycotic nodules projected into the cavities of the heart and coronary veins.

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Symptoms.—Symptoms of myocardial actinomycosis are very apt to be obscured by those of the process in the lungs or other parts. They will depend, moreover, upon the character of the changes that have taken place in the pericardium or elsewhere, and hence cannot be predicated in each instance.

Diagnosis.—Diagnosis of this form of myocardial disease can only be surmised, not definitely determined. The appearance of cardiac incompetence or signs of pericarditis, in a person suffering from actinomycosis, would render probable the involvement of the cardiac structures and, therefore, of the heart walls.

Prognosis.—The prognosis must, of course, be inevitably hopeless, since we possess no means of successfully combating the disease.

5. **New-growths.**—These are both relatively and absolutely very rare in the heart. They may be of any kind, although some occur more often than others. The variety of heart tumors is shown by Berthenson's figures, who, out of 30 instances found 9 of sarcoma, 7 of myoma, 6 of fibroma, 2 of gumma, and 3 each of carcinoma and cystic tumors. Of these the cardiac cavities were invaded in 22 cases (Whittaker) as follows: right auricle 7 times, right ventricle 3 times, left auricle 7 times, and left ventricle 5 times. Lipoma and myxoma have also been met, but are still more uncommon than the forms already mentioned.

Malignant neoplasms possess the greatest interest to the clinician, since they are the most serious. Although too many have been reported to make them a clinical curiosity, still their absolute infrequency is shown by the fact that up to 1893, Tedeschi was able to find only about 80 cases in the literature. To these he added 3 of his own, and as others have been recorded since his paper appeared, it may be quite safely stated that the total number to date will fall not far short of 100. Carcinoma is more frequent than sarcoma, and yet the relative rarity of cancer of the heart is shown by the following figures: Koehler found but 6 instances among 9118 autopsies, Fanchon 6 in 8189 autopsies, Willigk 9 of the heart and 7 of the pericardium in 4547 autopsies. The infrequency of cardiac cancer may be still further judged by the fact that Willigk's 16 instances occurred among 477 cases of the disease in general. When we come to consider the two forms of primary and secondary cancer of the heart, it is found that primary cancer is by far the less frequent. Thus, Petit is said to have found but 7 instances recorded in the literature.

Etiology.—As has just been stated malignant growths in the myocardium are very rarely primary. The neoplasm is most commonly secondary to disease of the mediastinum or lung, but may be metastatic from distant parts. In some instances the growth invades the heart by direct extension. The disease may occur at any age, even in childhood, but is of course most frequent in middle age, the same as malignant disease of other organs.

Morbid Anatomy.—Malignant neoplasms, whether carcinoma or sarcoma, are usually secondary to malignant disease of neighboring or distant parts. They may occur in the heart as either a single growth or as multiple nodules, more often the latter. The disease seems to be situated rather more commonly in the right side of the heart, especially when it is metastatic. In not a few instances the growths invade both the pericardium and myocardium, and it is often difficult to decide in which of these two situations the disease is primary. Alexander Lambert has reported a case of sarcoma which he

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took to be primary in the heart wall, in which the myocardium and pericardium were thickly beset with innumerable nodules of varying size. The wall of the left ventricle was invaded through its entire thickness by the growth which had wholly replaced the muscle tissue.

The presence of multiple nodules throughout the heart causes great enlargement of the organ, and the pericardium may be filled with a bloody exudate in consequence of the invasion of the sac by the neoplasm. The tumor may obstruct the orifice near which it is situated, and, if the mass projects into the cavity, the endocardium overlying it may be eroded. As the cancer is most often of the colloid variety it is likely to give rise to metastases, and the pulmonary artery may be occupied by carcinomatous emboli, as in Osler's case.

Symptoms.—There is nothing at all characteristic of myocardial cancer. There may be evidences of heart weakness, the pulse may be accelerated and irregular; but as the location in the heart is usually secondary to disease of other structures, these symptoms may be attributed equally well to that fact. Precordial pain has been noted, and in such cases is probably to be referred to pericardial involvement. Lambert's patient, an Irish laborer, was able to work up to a few days prior to admission to the hospital, and died of pneumonia, for which disease he had sought treatment. There may be evidence of cardiac enlargement on examination, and should an ostium be obstructed there might be a murmur or other sign of interference with the proper function of the valve. Pulmonary embolism should be attended with phenomena significant of that catastrophe. Distention of the pericardium, with sanguineous fluid, would be shown by the usual signs of pericardial exudate.

Diagnosis.—This is either impossible or a matter of good fortune. It is extremely doubtful if primary cancer of the heart can ever be diagnosed with certainty, and except in unusually favorable cases even the secondary form must be inferred rather than determined with positiveness. Involvement of the myocardium may be surmised upon the development of cardiac symptoms, that are more severe or of another character than can be readily explained by mere weakness on the part of the patient; likewise, if precordial dulness becomes so increased as to point to distention of the pericardium with fluid, or if murmurs or other signs be detected which indicate obstruction of an orifice or leakage of a valve.

Prognosis.—This is absolutely hopeless, and, after signs of cardiac weakness have once set in, a fatal issue cannot be long delayed.

Treatment.—This, from the very nature of things, must be limited to the relief of symptoms and the sustaining of heart power.

6. **Echinococcus.**—This is both relatively and absolutely a very rare occurrence in the myocardium. Thus of 160 instances of this disease affecting other organs than the liver, the heart was involved in only 10 (Whittaker); while of 1862 cases of hydatids, comprised in the united statistics of Davaine, Cobbold, Finsen, and Neisser, there were but 61 instances in which the heart and bloodvessels were the seat of disease. As might be expected from the greater prevalence of echinococcus in Europe, we find that the recorded instances of hydatids in the heart have been on the Continent or in England. In the United States but a single instance appears to have been recorded, and that by Grulee.[1]

[1] *Surgery, Gynecology, and Obstetrics*, October, 1905.

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Etiology.—Echinococcus disease of the heart may be primary, as Grulee believed was the case in his patient, but is in the majority of instances secondary to hydatids in other parts. In either event the parasites are conveyed to the heart in the blood stream. Probably the chief reason why the myocardium is not more often affected, lies in the fact of the lodgement of the scolices in the capillaries of the liver, as shown by the great predominance of hepatic echinococcus.

Morbid Anatomy.—Echinococcus cyst of the heart may be either intramural or endocardial, and may vary in size from that of a bean to that of an orange. The number of the hydatids also varies much. There may be but a single cyst situated in the myocardium, or there may be many cysts occupying and completely filling a cavity, as in Vines' case. When found in the interior of the heart the cysts may be loose, as in Wilks' case, or pedunculated. Thus, Otto found a mass of hydatids which, suspended by five long threads from the Eustachian valve, hung down through the tricuspid orifice into the cavity of the right ventricle and interfered with the perfect closure of the valve. In Crowther's case the cyst had ruptured, causing occlusion of the right pulmonary artery and sudden death. In Grulee's case an intramural cyst had also ruptured and led to multiple hydatids of the lungs.

Symptoms.—These depend upon the seat of the cysts, whether in the wall or a cavity of the heart. They cannot be predicated, therefore, and indeed, are probably disguised by others pertaining to the disease in other organs. The fact of sudden death from blocking of a pulmonary artery by cysts in Crowther's case should be kept in mind, as well as the possibility of pulmonary echinococcus resulting from rupture of a primary hydatid of the myocardium, as in Grulee's patient. One should also remember that serious obstruction to the circulation may result from cysts situated in the interior of the heart.

Diagnosis.—This can only be inferred when, in an individual known to have echinococcus disease of the liver or other viscera, symptoms arise which point to possible implication of the heart. It is quite evident, from a consideration of the morbid anatomy, that a myocardial hydatid, save in extremely exceptional instances, must be a discovery of the pathologist and not of the clinician.

Prognosis.—This depends largely upon the seat and subsequent history of the cyst. Its rupture may cause death in the manner already stated, or be responsible for a secondary invasion of the lungs through which the life of the individual ultimately may be sacrificed. In most instances probably death is likely to occur, either directly or indirectly, through the cardiac disease, since it is not amenable to treatment.

Treatment.—It goes without saying that this must be purely symptomatic and directed to other conditions than those of the heart.

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CHAPTER IV.

ACUTE ENDOCARDITIS.

By WILLIAM OSLER, M.D., F.R.S.

Definition.—Acute inflammation of the lining membrane of the heart and its valves, an incident in an infection or a terminal event in some chronic disease, is characterized anatomically by vegetations, necrosis, and ulceration. Chronic endocarditis, which may be either a primary change or a sequence of the acute process, will be discussed with chronic valvular disease of the heart.

Classification of Forms.—A good working classification, either etiological, anatomical, or clinical, is not easy to make. According to the *nature of the infecting agent* we speak of streptococcic, staphylococcic, pneumococcic, rheumatic, typhoid, or gonococcic; according to *the character of the lesion*, of verrucose or ulcerative; according to the *severity of the symptoms*, of benign and malignant varieties.

There is always a lesion of tissue—erosion of endothelium, vegetative outgrowths, ulceration—and the danger depends, first, on the nature of the infecting agent; secondly, on the extent of loss of substance, and thirdly, on the state of the body, *i. e.*, blood defences. But in any case there is no *benign* or *simple* form. Endocarditis is always a serious lesion, if not immediately by loss of substance, etc., remotely by the sclerotic changes which it initiates, and which lead in a majority of the cases to retraction and insufficiency of the valve. The so-called benign endocarditis kills in the long run a very much larger number of persons than the malignant form. Nor is the term acute free from difficulties. Infectious endocarditis is usually an incident in some acute infection, and the duration is reckoned by weeks or by a few months, and yet there are cases in which the process is active and symptom-producing for eight, ten, twelve, or more months—an essentially chronic condition.

There are clinically four great groups of infective endocarditis:

I. The *simple* endocarditis of the general infections (rheumatic fever, scarlet fever, typhoid fever, etc.), and, as a terminal infection, of many constitutional disorders. In itself, as a rule, harmless at the time, it leads in many cases to sclerosis of the valves and to chronic heart disease.

II. The *ulcerative*—the lesion is part of a septicopyæmia arising in a local infection, a skin wound, the puerperal process, an acute bone disease, gonorrhœa, etc.; less often in septic processes without external lesion, as in pneumonia. The endocarditis is only an incident, although often a serious one, in the infection.

III. The *recurrent* endocarditis on the old sclerotic valves of chronic heart disease, a common form, which may be slight or severe.

IV. *Chronic septic* endocarditis, in which for many months a state with remittent or intermittent fever is caused by the growth of vegetations on the valves.

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In groups I and II the symptoms are part of an infection in which the endocarditis is an incident. In III and IV the symptoms are directly due to the focus of infection on the valves.

History.—Here and there in the sixteenth, seventeenth, and eighteenth centuries there are references in the writings of Guy de Chauliac, Boerhaave, Senac, Morgagni, and others to alterations in the valves or in the lining membranes of the heart. Cowper,[1] the anatomist (1666–1709), described disease of the aortic valve, and Vieussens, in 1715, noted the same lesion. It was not until the nineteenth century that endocarditis was recognized as a special affection. Allan Burns (1809), whose little monograph is a storehouse of valuable observations upon the circulation, recognized the importance of changes in the valves. Matthew Baillie, in the first illustrated work on morbid anatomy published in the English language (1799), figures very well the results of endocarditis.

Krysig, in 1815, recognized the association of rheumatic fever and endocarditis. It is not a little remarkable that Laennec, in the first edition of his immortal work, makes no mention of the subject, but in the second edition, 1826, he speaks of it. Our accurate knowledge dates from the work of Bouilland (1840), who for the first time dealt with the question in an exhaustive manner, and we may say that our modern knowledge dates from him. He recognized inflammation of the valves, cardiovalvulitis, its great importance, and the frequency of the association with rheumatism.

A new chapter was written by Virchow in his studies upon pyæmia and embolism, and the observation of Kirkes showed the great importance of the severer forms and of the relation of the vegetations to embolic processes. The infective character of endocarditis has only been fully recognized since the studies of Winge, Köster, and Heiberg, but with the revolution in technique effected by Koch the association of the lesion of the valves with microörganisms has been exhaustively obtained, and we now know that while any and every infection may be complicated with endocarditis, there are certain organisms, viz., those of rheumatic fever (as yet doubtful), pneumonia, gonorrhœa, and pyæmia, particularly liable to excite it.

General Pathology.—We still have much to learn about the conditions under which the endocardium is affected, but the following statements formulate our existing knowledge:

1. Infective endocarditis is a valvular, rarely a mural, lesion, and on the valves the closure lines are points of election, viz., on the aortic cusps a little below the free edge and on the auriculoventricular valves the auricular faces, a little distance from the margin. In the fœtus the right heart is most frequently affected, in the adult the left. Malformations, as, for example, the edge of an imperforate septum, and valves which have sclerotic changes are especially prone to be attacked.

2. Most frequently an incident in septicæmia, it is not always possible to say whence the infection has been derived. In almost any one of the ordinary febrile diseases endocarditis may be a complication, but it is particularly during childhood that we meet with it, and above all others in the rheumatic affections. The tonsils are probably the portals of entry for the microörganisms in this group, and also in the not infrequent cases in which we meet with endocarditis without recognizable cause.

[1] *Philosophical Transactions*, No. 229.

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3. Certain bacteria are much more prone to excite endocarditis than others. The streptococci and staphylococci (with which may be included provisionally the "micrococcus rheumaticus"), the pneumococcus, and the gonococcus, are the chief endocarditis-producing organisms. The typhoid bacillus, the tubercle bacillus, the organisms of plague, cholera, influenza, smallpox, typhus fever, measles, scarlet fever, dysentery, glanders, and Malta fever are much less prone to affect the valves. Even in an acute infection, typhoid fever, for example, when endocarditis does occur, it is not necessarily due to the special organism, but may be a secondary infection with streptococci or staphylococci. So far as we know, the protozoa do not themselves excite an endocarditis.

4. The liability to infection of the valves does not depend upon (*a*) the number of organisms circulating in the blood. In typhoid fever, in lobar pneumonia, in certain cases of septicæmia, there may be the most intense blood infection for weeks without endocarditis. (*b*) Virulence of the organism plays an important part. The most intense local infections are met with in the virulent septicæmias, gonorrhœa, etc. (*c*) The bacteria of certain diseases excite only the mildest type of the disease. In rheumatic fever and in chorea the local lesion is itself trifling and rarely associated with destructive changes in the valves. And yet these are the very organisms which have a special predilection for the cardiac valves. (*d*) We do not know what determines the settlement of the organisms on special valves or on special portions. The liability of the right heart in fœtal life has been attributed by Rokitansky to the much greater frequency of malformations; by Virchow to the difference in intra- and extra-uterine life in the work and blood pressure of the two sides; by Rosenbach to the more favorable conditions for growth of organisms, depending on the oxygen content of the blood in the two sides at these different periods. This latter view supposes a sensitiveness to deficiency of oxygen or richness of carbonic acid which has not been proved for the organisms which excite endocarditis.

5. The studies of Rosenbach, Ribbert, Wyssokowitsch, Prudden, and others[1] have shown that experimental lesions of the valves if made with proper precautions are not followed by endocarditis, but if done with unclean instruments, or if after the injury cultures of suitable organisms are injected into the blood, an inflammation follows. The injection of cultures alone is, as a rule, negative so far as the valves are concerned; but Poynton and Paine, Cole, and others have shown that endocarditis may be caused by the injection of organisms belonging to the streptococcus class and the one which is believed to be the excitant of rheumatic fever. The writer does not know that a valvulitis has been caused by any other organisms apart from preceding injury to the valve. Ribbert has shown that by injecting staphylococcus emulsion containing coarse potato particles, the mitral and tricuspid valves, but not the aortic, are affected. He thinks that the fine particles injure the endothelium at the lines of contact and permit the micrococci to gain entrance, or they may be forced in by pressure.

6. While the general belief is that the microörganisms settle directly upon the valves from the blood current, Koster suggested that the peculiar localization of the lesion might be due to embolism. From the vascularization of the valves this does not seem very likely, although Orth and Wyler suggest

[1] Analyzed by Thorel in *Lubarsch und Ostertag's Ergebnisse*, 9th Jahrgang.

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that in certain cases of recurring endocarditis in an old sclerotic valve it might be possible, as they contain many large and wide vessels.

7. Strain and tension have a definite importance in connection with endocarditis. The more common involvement of the mitral and aortic valves in extra-uterine life may here find its explanation, and the more frequent implication of the large anterior segment of the mitral. The aortic segments are of practically the same texture, etc., as the pulmonic, but they show much earlier signs of wear and tear in the form of slight thickenings and atheromatous changes. The lines of election on both the arterial and the atrioventricular valves correspond to the very points which bear the greatest strain and on which, if anywhere, the endothelium would first suffer.

8. The unsolved problems of endocarditis are: (*a*) The reason for the localization of the lesions. (*b*) The conditions which enable microörganisms to settle on the valves and cause inflammation—are they always local? May they not be associated with properties of the plasma, etc.? (*c*) Is the valvulitis ever embolic? (*d*) What determines the marked variations in the lesions in the rheumatic, pneumococcic, gonococcic, and streptococcic forms? What is the factor favoring ulceration? What is in favor of a chronic proliferative process? What is in favor of the simple verrucose form?

Morbid Anatomy and Etiology.—In addition to changes in the endocardium there are usually alterations in the myocardium and very often in distant organs. The endocardial lesions are three—verrucose vegetations, necrosis and ulceration, and proliferative changes leading to sclerosis—and to these three correspond the triple clinical picture, the slight symptoms of the simple form, the malignant endocarditis, and the chronic valvular lesion.

1. **Verrucose Endocarditis.**—The lesion is usually in the left heart, and more often on the mitral than on the aortic segments. The peculiar localization has already been discussed. The mural endocardium may be involved but rarely without that of the valves. The vegetations form small, bead-like structures, soft and of a grayish-white color; in other instances they are warty or cauliflower-shaped excrescences, sometimes pedunculated. The smallest vegetation consists of (*a*) blood plates, (*b*) fibrin seated upon (*c*) an endothelium which presents changes. Beneath some of the tiny vegetations the endothelium may appear normal, but, as a rule, it shows signs of proliferation. In stained sections microörganisms are usually, but not always, found. In a later stage at the site of attachment and in the neighborhood the fixed cells of the subendothelium show proliferation, but there is rarely any leukocytic infiltration. The cells grow into the thrombi, which gradually become organized hyaline, changes occur, and a small, nodular thickening is left. This is the common thrombo-endocarditis which we meet with in so many of the acute infections and in the bodies of persons dead of tuberculosis, cancer, etc. It is not yet certain that in all instances of this form microörganisms are present; it is possible that toxic bodies in the blood may damage the endothelium of the valves along the closure line. In the more intense forms of the disease, such as that which complicates rheumatic fever, the necrosis of the endothelium is more extensive, the vegetations much larger, and the reaction in the valve tissues much more severe. There is a striking difference in the histological picture of a *bead* of vegetation on, say, the mitral valve in a case of diabetes and the section of a *warty* vegetation in a case of rheumatic fever or chorea in a child. In the one there may be scarcely any tissue reaction; in the

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other the valve changes are intense. And herein lies the great danger in this form of endocarditis, since in direct proportion to their extent and activity is the liability to the secondary progressive tissue changes in the valve leading to contraction, thickening, and insufficiency. On valves affected in this way verrucose endocarditis is very common, and presents two peculiarities—the vegetations show more rapid changes, as the vascularization of the valve is greater, and there is a greater danger of widespread necrosis and ulceration.

2. **Ulcerative, Vegetative, and Necrotic Lesions.**—Both sides of the heart may be affected, the right in larger proportion than in simple endocarditis. Of 209 cases, aortic and mitral valves were affected together in 41, aortic valves alone in 53, mitral valves alone in 77, tricuspid in 19, pulmonary valves in 15, heart walls in 33, and in 9 cases the valves of the right side of the heart were affected alone. Macroscopically there are three types of lesions: (*a*) Ulcerative, causing extensive destruction of the endocardium, of the texture of the valve, or even forming a deep ulcer which may perforate the aortic ring or the septum. Often it is only a superficial erosion of the valve covered with a gray, diphtheritic-looking membrane, hence the term diphtheritic applied to this form; or an aortic or mitral cusp may be perforated or a valve aneurism is formed. The most extensive destruction may occur, or a segment is eroded completely; in one instance two of the aortic cusps had completely disappeared to the line of attachment, which was smooth, while the third segment was more than half destroyed. In some of these severe ulcerative forms there are very few vegetations. When upon the base of a mitral leaflet or near the aortic or pulmonic ring the lesion may be deep and destructive, forming what is called acute perforative ulcer of the heart. This type is most frequently the result of infection with streptococci or other pus organisms. The process may be very acute; in a case in which a large ulcer penetrated deeply into the muscular substance below the aortic ring the entire illness was within ten days. Septic emboli, hemorrhage, and suppuration are frequent with this form. On the other hand, it may last several months and without acute symptoms.

(*b*) Globose, grayish-yellow or greenish-gray vegetations projecting from the valves, often having a fungoid aspect and without much superficial ulceration, but with great necrotic destruction of valve tissue, leading frequently to perforation. Seen in pneumonia and in gonorrhœa this type is common, and while there may be high fever and septic features, emboli and hemorrhages are not so frequent. When of any duration, the vegetations are not infrequently encrusted with lime salts. The process may extend beyond the valves. In one case there were mycotic aneurisms of the aorta, while in another they extended along the pulmonary artery almost to the hilus of the lung.

(*c*) A proliferative form characterized by outgrowths from the valves, the chordæ tendineæ, and the mural endocardium. In all varieties vegetations occur, but in certain of the severer infections they are larger and the valves are encrusted with firm, yellowish masses, often hanging in tags from their edges or coating the chordæ tendineæ, some of which may be eroded through. The mitral orifice may resemble the mouth of a miniature cave surrounded with stalactites, and the tendinous cords resemble twigs encrusted with lime salts. They are solid structures, not friable, intimately united with the endocardium, and the whole thickness of the valve may be involved at the

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attachment. In long-standing cases the vegetations may be very large, dry, hard, yellow, and without adherent thrombi.

Portals of Entry of the Infection.—Practically in all cases the micro-organisms gain entrance through the skin or mucous membranes. In the important group of cases in which the endocarditis is secondary to bone lesions the primary source of the infection, although often obscure, has been through one or other of these channels.

Mucous Membrane.—(*a*) *Alimentary Canal.*—This is the most common portal of infection. In the mouth alveolar abscess and the necrotic changes associated with bad teeth are occasional causes. Pyorrhœa alveolaris, an almost universal malady after middle age, is rarely a cause of endocarditis. Possibly some of the unexplained cases may be due to it. The *tonsils*, the mycotic hot beds, are responsible for a great many cases, and if, as is now commonly believed, the infection of acute rheumatic fever is here nurtured, they take the first rank as sources of infection. Certainly from them may be cultivated at any time the very organisms most prone to excite endocarditis. Not many cases are met with in connection with affections of the œsophagus or stomach. Ulceration of the intestines, typhoid, tuberculous, or dysenteric, may be complicated with endocarditis. A very important group occurs in connection with infections of the bile passages. Appendicitis is a rare cause.

(*b*) *Genito-urinary.*—Gonorrhœa, abscess of the prostate, chronic cystitis, and suppurative processes in the kidneys are common sources. Postpartum infection contributes an important group of cases.

(*c*) *Respiratory Tract.*—Among primary foci may be mentioned suppuration in the nose and adjacent sinuses, affections of the larynx and trachea, and occasionally bronchiectasis. Infection of the valves is a common complication of pneumonia, while pleural suppuration is a rare cause.

Skin.—Many of the severest forms follow local skin infections—post-mortem wounds, an accidental cut or prick during an operation, or the most trivial trauma may be the portal of entry. As a rule, in these severe infections following skin lesions, the endocarditis plays a secondary part. The picture is that of an intense septicæmia. The primary wound may be slight and may have healed before the severe symptoms are manifested. The writer saw such an instance in 1903, and although endocarditis was suspected and the blood was for weeks swarming with organisms, there were no physical signs to indicate the extensive lesions found postmortem. Many of the worst cases are in association with these comparatively slight infections of the fingers, as in one remarkable instance, in which a stalwart young fellow with an old mitral lesion, following the cleansing and cutting of his nails by a "manicure," had paronychia, which excited a malignant endocarditis, of which he died. Erysipelas may be complicated with severe endocarditis.

Primary Endocarditis.—A primary endocarditis, the result of injury or of cold, has been described. It is not always possible to determine that the valve lesion is really secondary. In one of the most acute cases of ulcerative endocarditis in the writer's series no primary source of infection was found, but the tonsils were not examined, and it is not possible to exclude all foci. A small spot of necrosis of the jaw, an insignificant joint lesion in a child, a small area of bronchopneumonia, a prostatic abscess the size of a pea, may be the source. The so-called endocarditis from cold is probably always rheu-

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matic and of tonsillar origin, and it may occur in the febrile attacks of children as the result of slight and even overlooked tonsillitis.

Practically all cases of endocarditis may be regarded as secondary to an existing infection.

Endocarditis as a Terminal Infection.—In the hearts of persons dead of chronic affections of all sorts—tuberculosis, dysentery, gout, cancer, chronic nephritis, arteriosclerosis, diabetes, chronic affections of the nervous system—it is common to find on the mitral valves, less often on the aortic, tiny beads of vegetation festooning the segments in the usual situation. In these very small soft structures it is not always easy to determine the presence of micro-organisms, and it has been urged that chemical poisons may be responsible for the primary change in the endothelium of the valve. Of the whole group of terminal infections, pleurisies, pericarditis, enteritis, etc., this is the mildest, as the endocarditis rarely produces any symptoms, and is never responsible for the final event.

Rheumatic Infections.—All other causes sink into insignificance before the endocarditis-producing poison of this motley group. The researches described by Poynton in the article upon "Rheumatic Fever"[1] have brought us nearer the solution of one of the most important problems in pathology. The precise germ may not yet have been settled, but the evidence suggests that the group of disorders to which the name rheumatic is applied depends upon infection with organisms related to the streptococcus group. The examination of the vegetations in rheumatic affections has been made in many cases, and a variety of organisms has been described. A full discussion of the subject is given by Bulloch.[2] The reader is referred to the section by Poynton for a description of the organisms which have been found.

Portal of Entry of the Germs.—Opinion has centred of late years upon the tonsils as the chief source of the infection for the following reasons: (*a*) The widespread, almost universal involvement of these structures in young children; (*b*) the demonstration in them of the very organisms which have been isolated from the lesions of rheumatic fever; (*c*) the clinical association of tonsillitis and arthritis; (*d*) the frequency of tonsillitis as a link in the rheumatic chain in young children; (*e*) the beneficial results which have followed removal of these structures in persons subject to recurring attacks of arthritis. There are still many points to be carefully considered. Tonsillar infection is universal in childhood, while rheumatic infection, although common, only occurs in a comparatively small proportion of children. But the same holds good with many "facultative" infections which we carry about. Only a few get pneumonia of those who harbor the pneumococci; not all take typhoid fever who carry the bacilli; many have foci of tuberculosis who never become tuberculous, and it is quite possible that in the tonsils, the crypts of which are natural culture tubes, many harbor the germs of the rheumatic affections of whom only a few show the positive manifestations. Invasion is a question of lessened resistance, lowered phagocytic power. Localization, whether in the joints, the nervous system, the skin or elsewhere, depends on circumstances of which we are as yet profoundly ignorant; and the same must be confessed of the precise circumstances which determine the occurrence of endocarditis in any individual case.

[1] This work, Vol. II, Chapter XXV.
[2] Vol. ii, part i, of the new edition of Allbutt's System.

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With the following infections belonging to the rheumatic group endocarditis may be associated:

(*a*) *Tonsillitis.*—Many writers have called attention to the presence of valvulitis in this affection, particularly Haig-Brown[1] and the much lamented F. A. Packard.[2] It may not be possible to determine definitely the nature of a given attack of tonsillitis. The lesion may be slight and readily overlooked, or there may be nothing more than a diffuse reddening with œdema and relaxation of the fauces. Many of the obscure febrile attacks in children, lasting from five to seven days without any localizing features, are associated with a tonsillitis of a very mild character. In such an attack endocarditis may lay the foundation of subsequent valve lesion. And in how many cases of mitral disease, particularly in women, is the history negative so far as the ordinary endocarditis-producing diseases?

(*b*) *Arthritis.*—Of all manifestations of the rheumatic poison, this is the one with which endocarditis has been recognized as the most serious complication. In children the percentage of valve infection in rheumatic arthritis ranges from 60 to 80, in adults from 25 to 35. Of 360 patients with rheumatic fever, nearly all adults, admitted to the writer's wards at the Johns Hopkins Hospital during fifteen years, 35 per cent. showed organic valvular disease. As Bouilland stated in 1840, the rule is for endocarditis, with or without pericarditis, to occur in all cases of severe rheumatic fever. In children the endocarditis may be the chief manifestation of the infection in an arthritis so trifling as to be overlooked, a slight swelling of one ankle, a little redness of one knuckle, with a fever of only a few days' duration. It cannot be too strongly urged upon practitioners to watch with the greatest care every case of joint complaint, however slight, every manifestation, indeed, of obscure fever, in young children, since, as pointed out by Graves, the endocarditis may precede the arthritis.

(*c*) *Chorea.*—Sydenham's chorea is now very generally regarded as an infection very closely related to rheumatic fever. It is not improbable that it will prove to be one of the manifestations of this protean infection. The important point here is that whatever the nature of the poison may be, it is singularly prone to attack the valves of the heart. Some years ago the writer analyzed records of 73 fatal cases of chorea in the literature, and of these 62 had endocarditis. The frequency of this complication has been dwelt upon by all writers on the subject. In Thayer's recent study of 689 cases at the Johns Hopkins Hospital there were 190 cases, or 27.7 per cent., with definite valvular lesions and in 45 others, murmurs were present. The writer examined 140 children more than two years after the attack of chorea, and found that 72 presented signs of organic heart disease. Arthritis, chorea, and endocarditis form a clinical trio of every-day occurrence in children's hospitals.

(*d*) *Erythema.*—The rheumatic character of nodose and polymorphic erythema has not been demonstrated, but they may be considered here as having at least affinities or relations with the poison which we call rheumatic. The endocarditis which occurs in these conditions is usually simple, but the writer saw one instance of severe endocarditis in a patient with high fever, arthritis, and purpuric urticaria. Many cases of endocarditis in erythema nodosum have been reported by French writers.

[1] *Lancet*, 1886. [2] *Transactions of Association of American Physicians*, 1899.

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(e) *Subcutaneous Fibroid Nodules.*—The association of these with endocarditis may be stated: (1) In children they are rarely met with apart from endocarditis. (2) In an immense majority of all cases in children they are a manifestation of the rheumatic poison. (3) They may occur in other than rheumatic forms, and in some of the most extreme cases there has been no arthritis, simply the nodules and a valvulitis, almost invariably mitral. There are varieties which have a very special relationship with certain forms of endocarditis, and will be referred to later.

Character and Results of the Endocarditis in the Rheumatic Group.—In a majority of instances it is an attenuated virus, producing the common verrucose form, with vegetations a little larger and more cauliflower-like than in the terminal endocarditis. There are four dangers associated with the lesion: (1) A vegetation may break off and cause embolism, a rare event in acute simple endocarditis, more common in the ulcerative form. (2) Recurring endocarditis. Recovery takes place, but fresh crops occur from time to time. (3) Proliferative valvulitis. As already mentioned, the substance of the valve is apt to be involved and the newly formed granulation tissue cicatrizes with puckering, contraction, etc., so that the function of the valve may be damaged very quickly. Within three months of the onset of the illness the leaflets of the mitral may be so curled and folded that not a fourth of their substance remains. (4) Ulceration and destruction of the valve, while not common, occur in a considerable number of cases. There were 24 among the 209 cases analyzed from the literature. Extensive ulceration is a rare event in the endocarditis of childhood.

The special danger, the danger that makes rheumatic fever one of the most serious of all diseases, is the starting of proliferative changes in the valve substance itself, which is gradually followed by cicatrization, with stenosis and insufficiency of the valves.

The Eruptive Fevers.—In *measles* endocarditis is rare, and when it does occur is an incident or a complication, such as bronchopneumonia, and is a streptococcic or pneumococcic infection. In *scarlet fever* it is more common, and occurs in connection with the angina or arthritis. It may be severe and part of an endopericarditis of great intensity. It is rarely of the ulcerative form. In *smallpox*, with such widespread suppuration, one would suppose that endocarditis would be a frequent complication, but it is rare. A systolic murmur at the apex is common as a result of the fever and of the muscular weakness, but it usually disappears. Ulcerative lesions have been described in a few cases, but the simple form is the most common. In chickenpox, mumps, and whooping-cough, endocarditis is not often met with.

Diphtheria.—Both forms have been described, but even in the several types of the disease the valves are not often affected. In 30 autopsies upon cases of a very malignant type the writer found no valve lesions other than the little nodules which seem more common in this than in any other disease. The diphtheria bacillus has been found in the vegetations by W. T. Howard and others, both in the verrucose and the ulcerative form.

Typhoid Fever.—Among 1500 cases there were only 3 with a diagnosis of endocarditis clinically, and among 105 autopsies there were only 3 (a total of 6 in 1500 cases).[1] Typhoid bacilli have been found in the vegetations;

[1] McCrae, this work, Vol. II, p. 145.

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clinically the complication is usually without symptoms, although in a few instances severe features have indicated the existence of an ulcerative form. It is to be remembered that many of the older cases of typhoid fever with endocarditis were probably cardiac from the outset. In *typhus fever, relapsing fever, cholera, yellow fever, Malta fever,* and *sweating sickness* endocarditis is an occasional complication.

Septicopyæmic Processes.—The most intense septicæmia may exist without endocarditis; the blood may literally swarm with streptococci or pneumococci for weeks without any affection of the valves. The lesions may be verrucose, but in this group we see the most severe types of ulceration and destruction, with embolic and septic changes in the organs. The infections of this class may be grouped as follows: (*a*) *Erysipelas,* in which the valvulitis may be of either form, but it is not a very frequent complication. (*b*) *Puerpural infections:* Many of the worst cases we meet with follow postpartum septic processes in the uterus or adnexa. Virchow figures a characteristic lesion in his well-known studies upon the subject. It is usually the ulcerative form, and often overlooked clinically in the intensity of the general infection. Eleven per cent. of the 209 instances of malignant endocarditis which the writer analyzed from the literature came in this class. Perhaps more often than in any other condition is the right heart affected. (*c*) Acute bone lesions and osteomyelitis are often complicated by ulcerative endocarditis. The cases are very numerous in the literature. (*d*) *Skin infections,* the septic wounds from whatever source, postmortem cuts or pricks, accidental infection at operation, paring a corn, etc. This is an important group and the endocarditis is usually severe. (*e*) *Miscellaneous infections:* Suppuration in the genito-urinary tract, in the liver and bile passage, abscesses in the abdomen, particularly the old peri-appendicular variety, empyema (rarely), fœtid bronchiectasis, a suppurating bronchial gland, a suppurative tonsillitis, etc.

Gonorrhœa.—Only of late years has it been recognized that one of the most common and serious forms of endocarditis was caused by the gonococcus. It is not easy to estimate the relative frequency, as the determination of the organism is not always easy. At the Johns Hopkins Hospital our attention was called to it by the work of Thayer and Blumer, who first demonstrated the gonococci in the blood. The literature is very fully given in *Lubarsch und Ostertag's Ergebnisse, Jahrgang* ix.

The valvulitis may be an incident in an early and intense gonorrhœal septicæmia, but more commonly it is a complication of the first ten weeks. A few cases have been reported as late as from the third and the fifth month after infection. It does not appear to have any special relationship with the arthritis. Women are rarely affected. The valves of the right side of the heart, and particularly the pulmonary, are perhaps more often affected in this than in any other form. While simple verrucose endocarditis may occur from which recovery takes place without much damage to the heart, this form is apt to be of great severity, associated with high fever, chills, sweats, and hemorrhages, with the embolic features of the most malignant types of endocarditis.

Tuberculosis.—Endocarditis is not very infrequent; the writer found 12 cases in 216 postmortems in the literature. G. W. Norris collected 151 cases in records of 11,000 autopsies in cases of tuberculosis. It may be (*a*) the terminal thrombo-endocarditis; (*b*) simple, warty endocarditis due to strep-

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tococci or staphylococci; (*c*) true tuberculous endocarditis, with tubercle bacilli in vegetations which have proved infective to animals. Ulcerative forms are exceedingly rare.

Malaria.—Except as a terminal event in the cachexia, endocarditis is an exceedingly rare complication of this disease. The frequent reference in older writers was due to an error in diagnosis, particularly in connection with the more chronic form of endocarditis associated with chills and fever. Among the many hundred cases of all forms of the disease studied at the Johns Hopkins Hospital there was not an instance of endocarditis.

Influenza.—A good many cases have been reported clinically, and a few in which anatomically the influenza bacillus has been found in the vegetation, in other instances in association with streptococci or pneumococci.

Symptoms.—A majority of the cases present no symptoms. The terminal endocarditis of the chronic diseases, the slight attacks of many febrile disorders, and even the complicated valvulitis of a septicopyæmia may give no indication of their presence, either by subjective sensations or by physical signs. The cases may be considered in three groups—the simple warty endocarditis, the acute ulcerative forms, and the chronic septic endocarditis.

Simple Endocarditis.—Fever is the most important single symptom. As a rule, it is already present in the disease in which the complication occurs, as in rheumatism, pneumonia, etc., but with the onset of the valvulitis the temperature rises or changes in character. The terminal thrombo-endocarditis may be afebrile; on the other hand, the slight rise in temperature for a few days before death, not uncommon in chronic nephritis or any protracted illness, may be associated with the occurrence of vegetations in the valves. The recurring endocarditis on the old sclerotic valves of aortic or mitral insufficiency may be indicated only by a slight pyrexia. The old hospital patients with these affections return again and again with slight febrile attacks or with transient cardiac insufficiency and an elevation of temperature for a week or ten days. In several such instances sudden death has occurred, and the only lesion to account for the fever has been the beady valvulitis on the old sclerotic segments.

After all, it is in children that endocarditis is a serious affair—perhaps *the most serious single infection, responsible for almost as many deaths as all of the exanthematous affections of childhood together*—and in them fever is *the* symptom. A chill at the onset is very rare. It is not easy, nor always possible, to distinguish the fever of the primary disease from that of the complication, as for example in rheumatic fever, when the disease is at its height, a loud, systolic murmur has appeared under observation. But when the arthritis has subsided and the temperature has fallen a recurrence of the fever alone with the characteristic physical signs is the best indication that valvulitis is present.

So, too, in other affections, *e. g.*, tonsillitis, the same rule holds good. There is nothing characteristic in the fever—a daily rise of from 1° to 3°, following the diurnal range. A sweat at night is not uncommon. The temperature may keep above normal for weeks; in fact, there may be nothing but the slight elevation to indicate that anything is the matter.

Does a growth of vegetations on the valves ever take place without fever? Not often in children, although it may be possible; but in adults even the worst types may be afebrile. Headache, loss of appetite, and the usual

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accompaniments of slight fever may be present. Symptoms pointing to involvement of the heart are inconstant. There may be no complaint to call attention to this organ. The *pulse* rate is increased with the fever, and in a few instances it becomes small and irregular, but there is nothing suggestive or characteristic. *Pain* about the heart is rarely complained of in the simple form occurring for the first time with rheumatic or other fever, but in the recurring endocarditis of old mitral or aortic disease, pain, even anginal in character, may occur with the febrile paroxysms. More commonly there is slight precordial distress. With pericarditis pain is more frequently met with, but the most severe endocarditis may be latent. *Palpitation* may be complained of, less often in children than in adults, and it may be associated with a transient oppression of breathing or a desire to sit up and take a deep breath. Disturbance of the skin sensations may be present—sensitiveness on pressure about the nipple or in the pectoral fold.

Physical Signs.—Inspection.—In children with fever the heart's action is usually forcible and the impulse is visible in the fourth and fifth interspaces, and in thin chests, even in the third. Much may be gathered from careful inspection of the precordia. The position of the apex beat, the character of the impulse, its extent and nature, indicate the state of the heart wall, and are measures to some extent of the severity of an endocarditis. As already mentioned, the little chaplet of vegetations does not represent the whole affair in endocarditis, but the heart muscle is often affected, weakened by the fever when high and still, more by a myocarditis, if present; and these changes are expressed by differences of the impulse and a slight dislocation outward of the apex beat. But it is more particularly with reference to prognosis that inspection is of value. For example, after an attack of rheumatic fever in a child, in whom an apex systolic murmur is present and persists, if when lying recumbent and straight the apex beat is within the nipple line and not forcible, we may feel confident that the damage to the heart is not serious, and even though the murmur persists there is not much if any valvular insufficiency. On the other hand, with the apex beat forcible, in and outside the nipple line, we know that serious damage has occurred and that the organ is crippled. In fact, inspection in heart disease often gives data of more value than those obtained by any other way, as they are less liable to misinterpretation.

Palpation.—Increased force and extent of the impulse are usually present, and the shock of both sounds may be felt. The shock of the second sound may be felt in the second left interspace. A thrill is very rare, but in a violently acting heart during high fever, a vibratory sensation is sometimes to be felt which simulates a thrill.

Percussion.—With involvement of the myocardium and consequent dilatation there is increase in the cardiac flatness, best appreciated by mediate percussion, upward and to the left. Increase to the right is not so easily determined. In many cases no change is to be determined. The personal equation has to be taken into account, and there are men with deft fingers and keen ears who recognize very slight alterations in the cardiac outlines.

Auscultation.—A majority of cases of acute endocarditis are on the mitral valves, and the most constant physical sign is the occurrence of a systolic murmur at the apex region. Two circumstances have to be remembered in connection with the diagnosis of endocarditis. In children and young adults with thin chests it is very common to hear a murmur at the second left

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interspace, which is of no moment whatever, and in fever with a rapidly acting heart a systolic bruit is usually present. The presence of a murmur then is of itself no indication that endocarditis is present, particularly if it is loudest over the body of the heart and at the pulmonic area. The murmur that is of moment in a given case, say rheumatic fever, has the following characters: (*a*) It has come on under observation and may have developed directly from a roughness or blurring of the first sound. (*b*) It is apical, below the fourth rib, often most intense upon it, but is also loud at the apex and is transmitted as far as the midaxillary line. (*c*) Soft and whiffing in quality at first, it may change under observation and become harsher. (*d*) It is present in the recumbent, sitting, and erect postures, often most intense in the first named; and (*e*) lastly, and most important of all, it is permanent. After all the symptoms have gone it persists and may increase in intensity. These are the important features in the simple form of mitral valvulitis met with in the acute infections, particularly in rheumatic fever. It is important to bear in mind that in a considerable proportion of all cases the condition is latent, and it may be accidentally discovered weeks after the original illness that the child has a valve lesion.

Infection of the aortic segments is much less common and, except in adults, is rarely met with alone. It is still more difficult to recognize. A systolic bruit at the base is very common in febrile states, and there is nothing to distinguish the murmur of rapid action and of altered blood states, etc., from that of a valvulitis. Only after convalescence may the persistency of the murmur, the increased vigor of the apex beat, and the slight extension of the cardiac dulness determine the diagnosis.

Simple endocarditis of the valves of the right side of the heart is of rare occurrence and still more rarely recognized.

Termination.—(1) The vegetations may disappear completely and leave no damage. Probably this is the case only with the slighter forms of thrombo-endocarditis, in which it may be shown histologically that there is little or no change in the valve tissue itself. (2) The vegetations themselves may gradually disappear, but the condition has been one of infiltration of the delicate membrane, and there is permanent damage caused by the shrinking and thickening of the tissues in a chronic, progressive valvulitis. (3) The vegetations increase in luxuriance, and the infiltration of the tissue leads to necrosis and ulceration. This is comparatively rare, as in only 24 cases of the writer's series did ulcerative endocarditis occur in rheumatic fever, and which may reasonably be supposed to have followed directly upon the simple form. (4) And, lastly, a fragment of vegetation may be whipped off, with the result of embolism in one of the arteries of the brain, the liver, the spleen, etc.—a comparatively rare event in the simple endocarditis of the fevers, but common enough in the recurring form on old sclerotic valves.

Complications.—Sturges very correctly insisted that a majority of the cases are best described as *carditis*, so frequently are the epicardium and the substance of the heart involved. Pericarditis is very common, particularly in rheumatic fever. Sibson[1] found 54 instances of pericarditis among 161 cases of endocarditis. As a rule, it is readily recognized by the presence of the characteristic rub, and is usually of the simple form without much effusion. Myocarditis is an almost constant accompaniment of endocarditis,

[1] Reynolds' *System of Medicine*, vol. iii.

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more particularly the rheumatic form. The feebleness of the pulse, the cardiac irregularity, the precordial distress, and the dyspnœa are features associated with this complication. Very rare complications are acute aortitis and rupture of one of the chordæ tendineæ. Of other complications, pleurisy and pneumonia are most common, particularly in the rheumatic cases.

Malignant Endocarditis.—It may be questioned whether it is worth while to consider the protean aspects of this infection under diseases of the heart, since the manifestations are those of septicopyæmia; and in a great majority of all the cases the features of the general infection dominate the picture. The clinical features are much influenced by the character of the infecting organism. The pus producers present a picture of severe and rapid pyæmia, with chills, fever, suppurative infarcts, and hemorrhages, symptoms which are associated with ulcerative lesions and numerous septic emboli. In the non-suppurative forms, the features, as a rule, are less intense, the cardiac symptoms more marked, and the picture is that of a septicæmia, as indicated by high and irregular fever. But there is no end to the diversity of the symptoms, and it does not seem possible to make always a separation between the suppurative and the non-suppurative varieties. Writers have been in the habit of grouping the cases according to the dominance of certain symptoms: (1) *The pyæmic form:* In this there is usually the well-marked local infection (an external wound, the septic uterus, an acute necrosis), but in other instances there is no definite focal lesion. Chills, sweats, high fever, progressive anæmia, wasting, with embolic features such as hemorrhages, bloody urine, pain over the spleen with enlargement of the organ, in some cases blocking of the larger vessels causing hemiplegia, or, in the large arteries of the limbs, gangrene, are the important symptoms. The heart features in this group are very variable. They may be marked—a loud murmur may develop under observation, and increase in intensity, changing in quality, and there are signs of dilatation of the heart. Or, under observation in the course of a few days an aortic diastolic murmur may arise. Under these circumstances, with a local lesion or in a *postpartum* case the recognition is easy enough. But in another group of cases the cardiac features are those of the ordinary intense febrile state—a mitral or a basic systolic murmur, not of great intensity and presenting no special characteristics. And lastly, with the most extensive valvulitis there may be neither symptoms nor physical signs pointing to the heart. (2) *Typhoid group:* Absence of detectable local focus of infection, irregular fever, delirium, dry tongue, occasional chills, perhaps diarrhœa, suggest the diagnosis of typhoid fever. Many of the severer forms of pneumococcic and gonococcic endocarditis are of this type. Embolic features are not so common, but there may be the same difficulty in determining whether the heart is really involved or not. It is in this group of cases particularly that the blood cultures are of the greatest value, and the evidences obtained from lumbar puncture. But even the most skilful diagnosticians may be in doubt, and it may not be possible to say anything more than that a condition of septicæmia is present. The illness lasts for from three weeks to three months, and the diagnosis may be made clear at any time by an embolic accident. Sometimes the whole picture is that of a meningitis. Even when no exudation is present, the headache, the progressive stupor, the cutaneous hyperæsthesia, and the rigidity of the neck may strongly suggest it. It is to be remembered that in the pneumococcic form, and in others,

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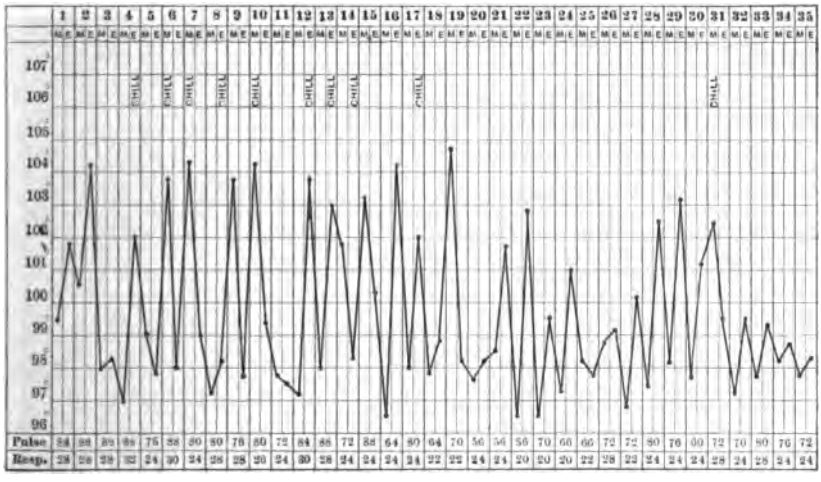
too, meningitis is by no means a rare complication, and in several instances in which this complication occurred early it led to an erroneous diagnosis. Practically these two types, the pyæmic and the typhoid, correspond to the two divisions of the suppurative and non-suppurative lesions.

A very interesting group of cases, the only one in which the diagnosis is easily recognized, is that to which Bramwell gave the name of (3) *cardiac group*, but which may be well called the *recurrent form*. In this the patient with chronic valve disease, mitral or aortic, begins to have irregular fever and an evening exacerbation of two or three degrees, an increase, perhaps, in his cardiac symptoms, and then embolic phenomena occur. The spleen enlarges and is tender, or there is pain in the back with bloody urine, or a sudden hemiplegia or a peripheral embolism may occur with gangrene. Such cases are very common, and while in some the process is acute, in others the symptoms may last for weeks or even months. These

FIG. 2



Temperature curve in a severe attack of endocarditis

are the cases, too, in which after the severest symptoms recovery may take place. The chart given here shows the temperature record of such an attack in a man with mitral stenosis, who was under the writer's care on and off for many years and who had several attacks of severe endocarditis, from which he recovered. This form, in which the patient has successive attack, in the intervals of which he is afebrile and fairly well, is common enough as an incident in old cardiac lesions.

An *afebrile form* has been described, and we must recognize that a chronic septicæmia may be present associated with endocarditis in which there is little or no fever. Even the very severe type with marked toxæmia may be afebrile. Such a case has been reported by O'Donovan, of Baltimore, and lately a most distinguished London physician, himself a keen student of heart diseases, succumbed to an endocarditis lasting several months, practically afebrile, and without special cardiac symptoms.

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Chronic Septic Endocarditis.—In reviewing the literature for the Gulstonian lectures on Endocarditis (1885), the writer was impressed by the protracted histories given by such keen observers as Wilks and Bristow. The chills, often recurring with great regularity, had suggested in these cases the existence of malaria. Bristow's case lasted for more than five months. Since then the writer has had a series of remarkable cases of what may be called the chronic septic endocarditis, in which the condition has persisted from periods ranging from four months to a year. Two of these were reported in the *Practitioner*, 1903. The main features are: (*a*) The presence of an old valvular lesion, aortic or mitral. An important point is the absence of any special change in the condition of the heart. In one patient, who had been under personal observation for a mitral insufficiency for fifteen years, at the end of a period of five months of daily fever (and nothing else) the condition of the heart was very much such as it had been years before, and yet the autopsy showed most extensive vegetative endocarditis. (*b*) Fever, which may be and often is the only symptom, with a daily rise of from 2° to 3° degrees. The chart shows an up-and-down septic temperature. Occasionally there are chills, but there may be fever of even a year's duration without any rigors. (*c*) Emboli are rare, but toward the close there may be high fever, petechiæ, and profuse sweats. Painful subcutaneous nodules of a peculiar form may be present, not exactly like the fibroid nodules of rheumatic fever, but rather resembling minute emboli of the skin. The spots are painful, reddish, slightly raised, and disappear in a day or two. (*d*) Anatomically the valves are found laden with vegetations, and the chordæ tendineæ are encrusted and often eroded. Infarcts are found in the spleen and kidney, but suppuration is not present. Pneumococci, streptococci, and staphylococci have been found in the vegetations. The cases appear to be more common in private than in hospital practice. The infection may persist for from three to four months to a year. In one of the cases reported, and of which the writer has a complete temperature chart, the fever lasted within two days of a year. In another the patient had a daily rise of temperature from the first week in December to September 16, nearly ten months.

Diagnosis.—There are two great groups of cases in the severer types. In the one endocarditis is only an incident in a general disease, and there may be no question of diagnosis, as nothing whatever in symptoms or physical signs may suggest endocarditis. It is surprising, indeed, in how many cases, particularly in pneumonia and in streptococcus septicæmia, the cardiac state is latent. The important points in the diagnosis are: the existence of a septic focus and a septic state, as indicated by the temperature, the blood cultures, etc.; the presence of petechiæ and embolic features, and the symptoms and physical signs pointing to a valvular lesion. Where the septic element dominates, the endocarditis is usually overlooked. When the cardiovascular features are well marked the diagnosis is usually made.

In the second great group, in which the vegetations form the focus of a chronic septicæmia, the diagnosis is by no means easy. The patients are the subjects of an old although often overlooked and well-compensated valve lesion. The fever begins insidiously, and for weeks the case may be treated as one of typhoid fever or the beginning of tuberculosis. Formerly malaria was suspected, but nowadays that is easy to exclude. Week after week, month after month, the daily rise of temperature may be the only feature,

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and, indeed, the patient may feel pretty well and be up and about for many weeks. The heart may present little or no change. An old apex systolic murmur indicating a mitral insufficiency may remain much the same. There may be very little enlargement of the heart. In the instance of aortic insufficiency the physical signs, as a rule, are more striking, the enlargement of the heart greater, and altogether the cardiac side of the case is more in evidence. So little change may there be in the state of the heart that on some occasions the writer had difficulty in persuading the attendant physicians of the serious nature of the cases until embolic features occurred.

Prophylaxis.—Much could be done to lessen the number of cases of rheumatic fever, of chorea, and of endocarditis if we attacked more vigorously and more systematically the enlarged tonsils of children. Here is the point toward which our efforts should be directed. A child subject to recurring attacks of tonsillitis, or with marked adenoids, should have the tonsils or adenoids thoroughly removed. Other measures of local treatment simply trifle with what is always a very dangerous condition. Physicians should be on the alert at the first indication of arthritis in the child to insist on absolute rest and to push the salicylates actively.

Treatment.—At the outset it may be questioned whether in endocarditis any measures are at our disposal worthy of the name of treatment. He must, indeed, have keen optimism who believes that we have any drug capable of influencing the state of the vegetations, the proliferative changes in the valve substance, or the mycotic destruction of the segments. In a case of simple endocarditis, particularly in rheumatic fever, the essentials in treatment may be briefly stated: Protracted rest which favors the restitution of the valve to its normal state. Probably the very slight warty growths may disappear without leaving any valvular thickening, but when there is infiltration of the tissue of the valve itself, sclerosis is an inevitable sequence. It seems absurd to talk about rest to structures which seventy or more times in the minute have to bear the full pressure of a ventricular systole, but it is relative rest if we diminish by one-third at least the amount of stress and strain which the mitral segments have to bear. This may be done by keeping the child at rest in bed. To be of any service it should be over a period of at least three months from the date of the fever.

Iodide of potassium may be given in moderate doses, in recognition of its control over vascular metabolism, a point which has been well brought out in these recent experiments upon experimental arteriosclerosis. Caton, of Liverpool, strongly recommends the application of small blisters over the heart. The writer has used these persistently in many cases, but is not able to say that any satisfactory results were evident. When there is distress about the heart, or palpitation, and particularly if pericarditis is present, an ice-bag may be used. When we can cultivate the organism of rheumatic fever and prepare vaccines, there may be some hope of mitigating and lessening the ravages of one of the most serious diseases of childhood.

The severer types of endocarditis are at present, in the majority of cases, entirely beyond our control. The treatment is that of septicæmia. In all cases with blood cultures an attempt should be made to determine exactly the infecting organism. A vaccine should then be prepared and used. The ordinary antistreptococcus serum which the writer has used in many cases has not proved successful in a single instance. There are instances, however, reported in which it has been successful.

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And yet the condition is not always hopeless. As is well known, cases of severe sepsis, more particularly puerperal, may recover, and there are a good many instances in which, with all the features of very severe endocarditis, recovery has followed. J. B. Herrick has collected a series of such cases,[1] and he has given anatomical evidence of the healing of serious ulcerative lesions of the valve. Recovery may follow in the gonorrhœal and in the pneumococcus forms, although this favorable termination is rare.

[1] *Transactions of the Association of American Physicians*, vol. xvii.

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CHAPTER V.

HYPERTROPHY OF THE HEART.

By ALEXANDER G. GIBSON, M.A., B.M., M.R.C.P.

GENERAL CONSIDERATIONS.

Introductory.—Hypertrophy, a property possessed by most organs of increasing in bulk, and allied in the lower forms of life to the function of reproducing lost parts, is in the higher forms restricted to the production of a greater capacity for total work in particular organs. Under the general term is included hyperplasia, an increase in the number of normal cells, and true hypertrophy, which is an increase in the size of the cells themselves. In the following pages the term will be restricted to its more general meaning, for we are not yet able to specify to what extent the two processes participate in hypertrophy of the heart muscle.

Taking the single cell, we do not know how this process of hypertrophy is effected, and indeed a purely theoretical question such as this need not concern us. From the standpoint of the organ and of the organism, however, its conditions are better known, as definite anatomical features accompany equally definite circumstances, and from a study of such it is possible to form some notion of the stimuli by which it is called forth. Let us therefore attempt to answer the question, *What is the immediate stimulus to hypertrophy?*

From the fact that hypertrophy of an organ is invariably accompanied by an increase in its activity and, conversely, that any increase in activity if persisted in over a moderate time is followed by hypertrophy, it is probably true that the two processes are bound up with one another; it might even be said that hypertrophy is the anatomical expression of the increased activity. Just as the contraction of a muscle becomes the indirect expression of the activity of a nerve, so it is legitimate to infer that an increase in activity will be followed by hypertrophy; hence, if the conditions of increased activity of heart muscle are inquired into, stimuli will be found which give rise to hypertrophy. Heart muscle can be stimulated directly or indirectly by means of nerves, and the direct stimuli are mechanical, chemical, thermal, and electrical.

Mechanical.—Such stimuli may be of various kinds, but that which concerns us here is mechanical stretching or an increased resistance to contraction.

In skeletal muscle it is a well-known fact that stretching, especially sudden stretching, can stimulate sufficiently to cause a contraction. This is the explanation of the knee-jerk; it is a direct stimulation of the muscle fibers of the vastus internus by a sudden tension of its tendon, the reaction time being too short to allow of a reflex taking place. The presence of an increased amount of urine in the bladder is associated with an increase in the rhythmical

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contractions of that organ. In the snail's heart contractions stop if the chambers are emptied by bleeding and begin again if pressure be again put into the system. Von Frey[1] has shown experimentally that an increase of resistance acts as a stimulus to the frog's heart and the amount of distention regulates the force expended in the beat. The time relations are too quick to allow of its being due to a reflex regulating mechanism, for the increase in force with an increase in distention often appears in the systole immediately following. Moreover, the mechanism is still present after the severance of all nerves. Of the relation of muscular volume to resistance, the conditions of the fœtal heart are instructive and conclusive; Gibson and Gillespie[2] have shown that before birth the walls of the ventricles of the heart are of equal thickness; after birth, when the two cavities are entirely cut off from one another directly, the right ventricle increases in thickness at a much slower rate than the left. In fœtal life the pressure in the two ventricles is approximately equal from the patency of the ductus arteriosus; after birth, when the umbilical artery is closed, the pressure in the right auricle immediately falls, the valve of Vieussens closes, and the ventricle requires no more, if as much, force to propel the blood to the left auricle through the lungs.

The increase of activity as a result of mechanical stretching is probably entirely apart from any nervous action, for Rieder[3] has shown that an increase in the work of the beat can be obtained even when all nerves are cut.

Chemical.—That a chemical substance circulating in the blood can increase the activity of muscle and cause it to increase in volume is probably true, but proof of it is not yet forthcoming. Of the substances to be thought of in this connection are veratrine, digitalis, adrenalin, and the cardiac tonics. A chemical element, again, may be present in renal disease or Graves' disease where heart changes occur, but the hypotheses of a chemical stimulus to heart activity in these diseases is as yet unproved; very significant is the recently established fact that renal disease with hypertrophy is always associated with hypertrophy of the suprarenal glands. It has recently been found[4] that repeated injections of adrenalin will produce hypertrophy, but whether from its action on the muscle or indirectly from the associated atheroma cannot yet be decided.

Thermal.—Such stimuli are difficult to discuss in relation to hypertrophy. An increase in the heart rate follows artificial raising of an animal's temperature. In fever the toxæmia introduces another element probably acting against any possible hypertrophy.

Electrical.—In skeletal muscles the value of galvanism in preventing or even overcoming atrophy of muscles in infantile paralysis is great. Whether this is a direct stimulation of the muscle fibers or of the muscle end-plate is not known; it serves, however, to show that a muscle can increase in size in the absence of its proper physiological stimulus. No observations on the heart muscle in this connection are forthcoming.

Nervous.—Muscular tissue can be stimulated to increased activity by nervous action. In heart muscle there is little direct proof of hypertrophy following increased stimuli because, if we take the myogenic hypothesis as

[1] *Deutsch. Arch. f. klin. Med.*, 1889, xlvi, p. 398.
[2] *Edinburgh Medical Journal*, 1892, xxxviii, p. 429.
[3] *Arch. f. klin. Med.*, 1895; quoted by Thorel in *Lubarsch und Ostertag's Ergebnisse der Pathologie*, 1904, p. 797.
[4] Grober, *Deutsch. med. Woch.*, 1907, xxxiii, p. 744.

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correct, the nerves of the heart have only a secondary effect in altering the muscle action. But considering skeletal muscle, ample proof is not wanting. If a nerve to a skeletal muscle be cut the latter degenerates, while if the nerves be more frequently stimulated, as, for instance, by electricity or by use, the muscle hypertrophies. In regard to the relation of nervous action to cardiac hypertrophy only indirect evidence is available. Hering has recently found that if the heart is in standstill, stimulation of the sympathetic nerve supply will cause the heart to beat; it has long been known that stimulation of the sympathetic nerves to the heart will produce a faster rate and a more powerful beat than in the normal condition. A few conditions met with clinically point to this cause as the origin of conditions of hypertrophy. In neuritic lesions of the brachial plexus, especially the left side, it is not unusual to find evidence of some hypertrophy of the heart (Potain). The slight hypertrophy that is met with in neurotic persons is probably of this nature. Moreover, such may be the cause of the hypertrophy that is found as a result of excessive sexual indulgence and that sometimes associated with growth.

Nutrition and Hypertrophy.—The relation between hypertrophy and hyperæmia is very close, and in heart muscle probably plays a very essential part in the ultimate establishment of that process. Instances in general pathology of hyperæmia causing hypertrophy are sufficiently numerous, as, for instance, after cutting the cervical sympathetic nerve on one side of the neck of a rabbit a more vigorous growth of hair on that side results. In skeletal muscle the sequence of events is probably this: increased activity of muscle from stimuli arising from motor nerves, increased contraction of muscle, afferent impulses then travel up and reflexly cause dilatation of the muscular arterioles, and the increased nourishment thus supplied causes a direct increase in the size and probably the number of the muscle fibers. By analogy the same process may occur in the heart; the increased contraction may be brought about by any one of the conditions just enumerated; this then causes reflexly a hyperæmia of the muscle and consequently an hypertrophy of the muscle fibers. Or another possibility is that the increase in aortic pressure produced by an increase in heart activity forces more blood into the coronary arteries. Albrecht,[1] from an examination of a number of hearts in which hypertrophy was present, strongly advocates the view that hypertrophy is a true inflammatory process or a proliferating myocarditis. He finds changes of the nature of hypertrophy to occur in the neighborhood of undoubted foci of inflammation. But it may be doubted whether Albrecht's view expresses more than a portion of the truth. If it be true that hyperæmia in heart muscle produces hypertrophy, then hyperæmia, whether general, as from reflex nervous processes, or local, as from a small inflammatory focus, will cause the muscle to react in the same manner in either case. Moreover, other authors[2] have not been able to confirm Albrecht's proposition that in hearts, *e. g.*, from cases of hypertrophy from renal disease, there are foci of inflammation, unless produced by an accompanying sclerosis of the coronary vessels. Krehl is of the opinion that increased nutriment of itself does not lead to hypertrophy of the heart, but only when it is associated with an increase of activity, for an increased pressure in the coronary arteries does not necessarily lead to hypertrophy of the right ventricle (*e. g.*, in renal disease).

[1] *Der Herzmuskel*, Berlin, 1903.
[2] See Aschoff and Tawara, *Grundlagen der Herzschwäche*, Jena, 1906.

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That hypertrophy is not dependent on general nutrition has been proved by Tangl, who, after producing an artificial insufficiency of the aortic valves in starving dogs, still found hypertrophy to occur.

HYPERTROPHY AS OCCURRING IN A NORMAL HEART.

The Relation between Muscular Work and Hypertrophy.—A number of conditions of life, chiefly those associated with muscular exertion, lead ultimately to hypertrophy of the heart. As Clifford Allbutt pointed out in 1870, many laborious occupations lead to marked hypertrophy and cardiac failure. When muscular work interferes with function it would be classed under cardiac insufficiency, which will be discussed later. We are, however, justified in thinking, from the results of certain observations which will be mentioned, unfortunately by no means complete as proof, that increased muscular work, when carried out under conditions which are within the physiological limits for the particular person, leads to a certain amount of cardiac hypertrophy—an hypertrophy which is associated with the necessity for a widening of the amplitude of cardiac response. Katzenstein[1] perhaps puts this view forward in the clearest manner when he says: "Lewy has reckoned that the sound normal heart does at rest 815 mkg. of work in the hour, with greater bodily exertion it does fourfold that amount, and can by still greater work set free thirteen times the first amount." Now, this property of the heart to be able to accomplish more than it has done at rest is called reserve power (Reservekraft). Also from this conception of reserve power that in life only shows itself on necessity, valvular failure, external bodily work, and so on, it follows that the heart does only so much work as in each moment it must.

In this relation it is absurd to suppose that an hypertrophied heart, that as yet really only possesses a greater breadth of reserve power than the non-hypertrophied, does more work than corresponds to its needs. The heart hypertrophied as the result of work (Arbeitshypertrophie) differs from the normal heart in that it possesses a much greater amplitude of reserve power, *i. e.*, the demand which can be put on the hypertrophied heart because of its breadth of reserve power is many times greater than in ordinary hearts. To take an example: it is both conceivable and highly probable that when an athlete undergoes severe training for a long race, while he widens the limits of endurance he puts on an additional weight of heart muscle. Race-horses and greyhounds which have been conspicuous in winning races have had notoriously large hearts. The increased work required from the athlete's heart, however, is only required during the period of activity, not when at rest, and so long as he trains without increasing the latter requirements, he trains well; but as soon as the exercise has an effect on the muscle so as to demand greater work at rest, so soon should training be stopped or abated. The average athlete's heart when examined at rest is not one which is acting vigorously; more usually his pulse rate is below the average, 50 per minute or even less; the pulse is not abnormally large in volume or high in tension, the apex may be difficult to find from compensatory increase in lung capacity, and the heart sounds are frequently more difficult to hear than in normal persons.

[1] *Dilatation und Hypertrophie des Herzens*, München, 1903, p. 58.

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Külbs[1] finds an increase in the weight of the heart in proportion to the degree of work performed. He took two pairs of dogs, the dogs in each pair being as nearly similar as possible in weight, build, and age. He then subjected them to exactly similar conditions, except that one was made to do work on an endless stage. In both experiments there was a marked increase in the weight of the heart in the animal that had done work. Thus the relation of heart muscle to skeletal muscle in the controls was respectively 1 to 53.9 and 1 to 59, and in the animals subjected to work 1 to 37.4 and 1 to 37.7 respectively—a proportion which is exactly that of the relation of the heart muscle to skeletal muscle in the deer. The increase affected the right as well as the left side. But the increase of heart muscle was much greater in proportion than that of the skeletal muscle. Thus in one pair the increase in heart weight was 53 gm. from 99 gm. (the weight of

FIG. 3

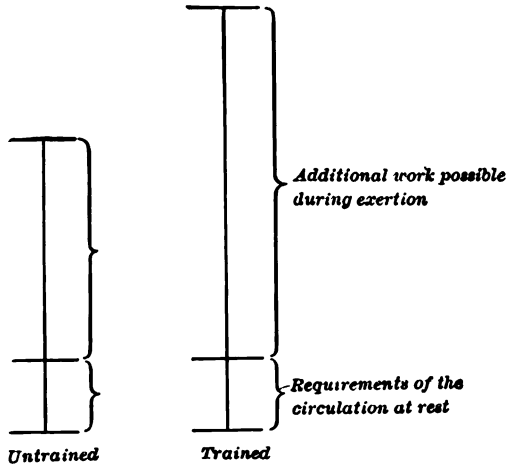

Diagram to show the difference between the heart of an untrained person and a trained athlete.

the control animal's heart) and the increase in skeletal musculature was 354 gm. from 5342 gm. (the weight of the control animal's musculature). If the skeletal musculature had increased in the same proportion as that of the heart it should have been 8201 instead of 5696 gm. in the working animal of the first pair and 10,313 instead of 6498 in that of the second pair. There was a marked increase in the weight of the liver, spleen, kidneys, lungs, and pancreas, especially the first; it is therefore possible that the increase in work of these organs from metabolic reasons requires a further increase in the heart weight.

Grober[2] has weighed the total heart and its parts of rabbits kept in confinement, wild rabbits, and hares, and finds a much heavier heart in the wild rabbits than in the tame and in the hares than in the wild rabbits.

[1] *Archiv f. experim. Path. u. Pharm.*, 1906, lv, p. 288.
[2] *Deut. Arch. f. klin. Med.*, 1907, xci. p. 502.

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This order corresponds with the degree of their muscular activity. The enlargement affects the right side of the heart more than the left; thus, in one instance quoted the left ventricle of the tame rabbit weighed 0.989 gm. while that of the hare weighed 2.840 gm., about thrice the amount; and the right ventricle of the tame rabbit 0.462 gm., of the hare 1.860 gm., more than four times the amount.

The foregoing facts are made clearer by a short survey of the weight of the heart in various animals and in man at various ages and under varied conditions.[1] Bergmann compared the weight of the heart to the total body weight and found that the fraction $\frac{\text{heart weight}}{\text{body weight}}$ became greater in proportion to the muscular activity of the animal. The following scale is arranged in consecutive order: Ox (gelded), 1 to 258; pig, 1 to 220; ox, 1 to 193; woman, 1 to 183; man, 1 to 170; hare, 1 to 132 to 1 to 140; and deer, 1 to 86.

Parrot, extending Bergmann's researches, found a much larger heart weight in proportion to body weight in singing and flying birds than in others. W. Müller found that in man the weight of the heart as well as that of its separate parts bore a very definite relation to the body weight and to the height, the heart weight increasing with age, size, and weight; the fraction $\frac{\text{heart weight}}{\text{body weight}}$ was proportionately less in women than in men. A few conditions only interfered with the general rule; in very fat subjects the fraction was much less; hence, probably the frequency of heart failure in these persons. In wasting diseases such as tubercle and carcinoma the fraction became less. There is still doubt whether the heart in pregnant women undergoes any increase, as was formerly accepted; a reëxamination in 22 cases by Hirsch has shown that the fraction remains about the same or is slightly less than for a series of non-pregnant women.

When the strain of muscular work is greater than it is possible for the person to withstand, owing to the continued high pressure in the cavities of the heart, there is a failure to expel the whole of the blood brought to the ventricle; the consequence is a dilatation of one or more of the cavities of the heart for the time and an interference with the proper action of the cardiac muscle. In such a person at rest, in order to expel the necessary amount of blood into the aorta, the heart at each systole would have to exert, by reason of the dilatation of its cavity, a greater pressure per unit area of its internal surface than a heart whose cavity was not so dilated. The amount of work therefore expended in such a heart per unit of time would be greater than in the normal heart even at rest.

However difficult such distinctions may be to recognize clinically, it is highly necessary to do so theoretically; for while the athlete whose heart requires no increase of work to carry on the bodily functions at rest is normal, the one whose heart is working more than it should do at rest is running a serious risk of heart failure in the near or remote future.

In this section it is desirable to treat only of those conditions in which there is no reason to suspect an increase of heart requirements during rest.

[1] See Hirsch, *Ueber die Beziehung zwischen dem Herzmuskel und der Körpermuskulatur und über sein Verhalten bei Herz Hypertrophie, Deutsch. Arch. f. klin. Med.*, 1899, lxiv, p. 596. Bergmann, *Diss.*, München, 1884, and W. Müller, *Die Massenverhältnisse des menchlichen Herzens*, Hamburg, 1884.

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The conditions under which normal hypertrophy occurs are:

1. The hypertrophy of growth.
2. From the use of ski.
3. In consequence of cycling.
4. In mountain dwellers.

1. **The Hypertrophy of Growth.**[1]—It has been asserted, especially by French writers, that children and young people about the age of puberty frequently show both objective and subjective signs pointing to an hypertrophy of the heart. Judging from the published accounts of the cases, the condition is one with occasionally some enlargement of the heart, especially to the right, with increased force of the beat, as felt in the chest. We require, therefore, further evidence on the point whether the heart at rest is acting with more power. Seeing, however, that it is a phenomenon seen in children with no suspicion of disease, it is well to insert it at this stage, and not leave it to be included among the abnormal causes of hypertrophy.

FIG. 4

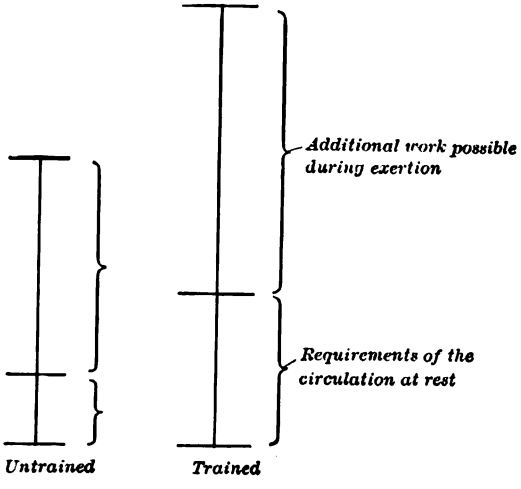

Diagram to show the difference between the heart of an untrained person and an athlete whose heart is beginning to enlarge as the result of overstrain.

2. **Hypertrophy from the Use of Ski.**—The use of *ski* for the purpose of locomotion is attended with but ordinary exertion on even ground, but in rough or hilly regions the efforts required are maximal. Henschen was able to determine in Laplanders the presence of hypertrophy of the heart; if not of the whole heart, yet certainly of the left ventricle.

3. **Hypertrophy in Consequence of Cycling.**—Schrieffer,[2] investigating by means of *x*-rays and percussion the size of the heart in young men of the age of military service, finds that habitual use of the cycle causes a definite increase

[1] See Romme, *Gaz. des hôp.*, 1896, p. 34. Beneke, *Centralbl. f. med Wiss.*, 1899, vol. xxxvii, p. 358.

[2] *Deutsch. Arch. f. klin. Med.*, lxxxix, 1907, p. 604.

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in the size of the heart area. He finds that even hard occasional cycling does not produce any result which can be determined by his method, but that if a cycle is used continuously for three years such evidence is always forthcoming, and if it is continued for a longer period the hypertrophy increases. Both the transverse and the longitudinal heart diameters of the *x*-ray picture are increased and consequently the total area. In 13 out of 35 men who had used cycles for three to fifteen years the superficies of the heart exceeded by 25.9 sq. cm. the normal (even up to 35 sq. cm. in some). The normal areas are obtained for the corresponding heights and weights from Dietlen's[1] figures. Whether the size of the heart's area is taken in proportion to the weight or height, it still shows an increased proportion from 5 to 29 per cent.

It is only right to say that Schrieffer himself believes that there is in all these hearts examined an abnormal dilatation, and that it is an abnormal condition. He supposes, although he has no direct proof, that such persons are more in danger of heart failure than others. From one point of view, however, being otherwise normal men in a healthy condition, they can stand as much strain as other young adults. But from clinical examination of the apex beat, percussion, auscultation, etc., a certain number are evidently abnormal. Thus, 4 out of 71 individuals had an apex beat outside the nipple line, 11 had it in the nipple line, 30 almost in the nipple line, while 20 had it within. In 14 there was a systolic murmur at the apex and 44 had an accentuated pulmonary second sound. It may be doubted if all these are normal, but it is probably right to assume that a certain proportion had hearts which showed no signs of dilatation or insufficiency at rest.

4. **In Mountain Dwellers.**—The volume of the heart muscle in animals, as is shown in Parrot's figures, bears a definite proportion to the amount of work which the animal's habits of life necessitate. The same has been shown for human beings living in mountainous districts as compared with those living in the plains. In the first place it is well known that heart failure is much more common in very mountainous districts than in flat countries. Mosso (*Der Mensch auf den Hochalpen*) mentions this fact, and that the majority of old persons die of heart-failure. The "Tübingen heart" is a classical example of heart failure the result of arduous labor in a hilly district. These facts suggest that in normal persons the heart must be heavier than in those who do no arduous daily work.

Kalmansohn[2] has investigated the hearts from 379 patients not dying of heart disease or associated with any obvious cause of hypertrophy. He finds that the average weight of the heart for corresponding age periods of twenty years is greater in Zurich than that obtained by Müller in Jena and Peacock in London. It affects women as well as men, but the former not so markedly—and the differences become less marked, especially in women over the age of forty years. In most of the patients no abnormality had been detected in the heart during life. We shall probably be right in assuming, as does Kalmansohn, that in them a larger amount of bodily exertion, both in their daily vocations and pleasures, necessitated an increase of muscular tissue in the heart.

Anatomy and Histology.—We have yet to learn from actual data whether in these cases the cavity of the heart is enlarged or not, whether such hearts

[1] *Deutsch. Arch. f. klin. Med.*, 1906, lxxxviii, p. 55.
[2] *Diss. zur Herzgewicht*, Zurich, 1897.

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are to be looked upon as concentrically or excentrically hypertrophied. Moritz conceives it impossible to have an increase in the size of the fibers of the heart wall without a corresponding increase in the internal surface; but the very fact of there being a concentric hypertrophy in the newborn child and in children up to the tenth year[1] suggests that an increase in growth is not necessarily associated with an increase in the size of the heart cavities. On the other hand, if we suppose that the tonicity of heart muscle is variable, it is probably true to say that when heart tonicity is great the muscular walls are well knit together and the cavities smaller, in the same manner as, for instance, in rigor, than when tonicity is at a lower level. Further work is required to give more insight into these conditions, and all we can suppose at present is that in the hypertrophy of work new relations are set up in the heart, which, with an increase in the bulk of its muscle, put no additional burden on the mechanism when the person is at rest.

FIG. 5

Heart of normal dog, 99 gm. Heart of dog subjected to work, 152 gm.

So little is known of the conditions that exist in man that what knowledge is available is derived from the study of the hearts of animals under experimental conditions. Külbs, for instance, in the dogs which have been subjected to work compared with dogs not so treated, finds the heart increased in size as a whole and showing an increased thickness of the walls of the left ventricle, right ventricle, and ventricular septum (Fig. 5). Grober finds that the right ventricle is increased more than the left, and mentions that in the animals of active habit the parts not weighed (auricles) appear to be increased in proportion to the others. Owing to the technical difficulties, nothing certain is known of the size of the cavities of the heart.

Histologically such hearts are sharply demarcated from hearts hypertrophied as the result of a valvular lesion. The fibers are not increased in size, nor do they show an increase in the amount of sarcoplasm. An increase of interstitial tissue is not present.

[1] Parrot, quoted by Thorel, *Ergebnisse der Pathologie*, 1904, p. 759.

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Diagnosis.—Ex hypothesi we have defined this type of hypertrophy as one which is developed only for special times during the period of exertion. Symptoms are therefore out of the question except during the period of exertion at the limits of cardiac endurance. Further, many of the usual signs of hypertrophy, increased power of the apex beat and accentuated second sound at the base, are probably not evidence of hypertrophy so much as of the overaction which is necessary even during rest to combat the effects of interference against which the hypertrophy is the normal reaction. We would arrive, therefore, at the opinion which is corroborated by physicians of the widest experience, that a heart which at rest gives signs such as a heaving or diffuse apex beat, with a strong pulse and accentuated second sound, is one which is less efficient than one in which the apex is localized

FIG. 6

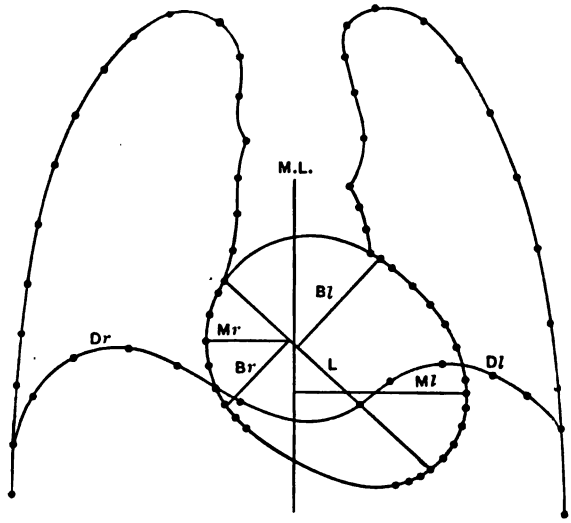

Diagram to show the method of measuring an orthodiagram of the heart: *L*, long diameter; *Br*, *Bl*, breadth to right and left sides respectively; *Mr*, *Ml*, breadth to right and left respectively, taken in the horizontal direction; *M L*, middle line; *Dr*, *Dl* = right and left sides of the diaphragm respectively. The dotted line shows the lines which are marked in at the time of taking the orthodiagram. (After Dietlen).

and not forcible, with no marked increase in pulse volume and with no accentuated second sound. In other words, an hypertrophied heart which is doing more work at rest than a normal heart is one which cannot run the same risk as one which does not show such signs.

Da Costa mentions the difficulty of accurate delimitation of the size of the heart, and asserts, what is highly probable, that hearts of very different size are put down as normal. With the use of the *x*-rays it is now possible to estimate with considerable accuracy the size of the outline of the heart as shown on the screen, and the results obtained amply justify Da Costa's supposition. Dietlen[1] has recently recorded his observations on the size

[1] *Deutsch. Arch. f. klin. Med.*, 1906, lxxxviii, pp. 55 and 286; see also Simons (p. 246) and Moritz (p. 277).

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of the normal heart by means of the orthodiagram, at the same time comparing with this the results of percussion. By means of this method he finds that a relation exists between the height and the dimensions of the heart area; similarly there is a variation with body weight, age, etc., bearing out exactly the results arrived at by Hirsch on the dead subject.

Dietlen's examinations were made on 187 men and 74 women, all free from cardiac or severe skeletal disease. He finds that the size of the heart varies somewhat with the height, but a much more constant relation exists between the weight and the size of the heart area; that the mammillary line bears no fixed relation to the height or weight, varying in men from 8 to 13 cm. from the midline; therefore information as regards the apex beat made with reference to the nipple line is not of much value. The size of the heart increases with age and sinks with the diaphragm lower in the chest. The apex beat is generally felt in the intercostal space above that in which by the *x*-rays the apex would be supposed to be.

Percussion of the heart in the hands of men who have tested their results by means of *x*-rays appears to give highly accurate results except in one or two conditions, such as emphysema of the lungs. No special form of percussion seems to give more accurate results than another. Goldscheider[1] has recently advocated the original method of Auenbrugger, of very light ortho-percussion. Ebstein recommends tactile percussion and Moritz the ordinary method with two fingers, using heavy percussion for determining the right border and medium or light percussion for the left, which is less easy to define.

HYPERTROPHY AS A DEFENCE AGAINST A PATHOLOGICAL CONDITION.

The hypertrophy we have previously dealt with has been such as only served to increase the total activity of the heart at certain times; we have now to examine the conditions under which for the proper upkeep of the circulation a constant increase in heart work is required. Broadly speaking, the one cause of such necessity is an increase in the residual blood in the heart chambers after systole; such an extra amount of blood, together with that which flows in during the diastole, requires a larger cavity at the beginning of systole than formerly. In order to effect the required transference of blood into the next chamber or tube the same pressure must be communicated to the liquid as before, this being given to the liquid by the contraction of the walls of the cavity. But in order for the amount of blood to be at the same pressure as formerly the same pressure per unit area of the internal surface of the cavity must be given as before; hence, if the internal surface is greater the total required is greater and the heart must beat more vigorously. But an increased activity when continued leads to hypertrophy. Such an example would apply to the conditions occurring after a lesion to a valve or a dilatation of the heart the result of a strain. If the lesion causes a permanent increase in the residual or diastolic blood in the heart, then the cavity of the heart is permanently enlarged and the hypertrophy which develops probably also permanent.

[1] *Deutsch. med. Woch.*, 1907, Jahrg. xxxiii, p. 1121.

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The dilatation would then be spoken of as compensatory, and although when compensatory dilatation becomes great, it may merge gradually into the dilatation associated with and accompanying some forms of chronic cardiac insufficiency, in the forms with which we are here dealing, in which the circulation is compensated for rest, it must be clearly distinguished from heart failure.

The accompanying diagram represents the conditions of the heart in three stages: *a* is a normal heart; *b* a heart with an increase of reserve power, a heart hypertrophied as the result of muscular exertion, and *c* is a heart which has undergone compensatory dilatation and consequent hypertrophy.

FIG. 7

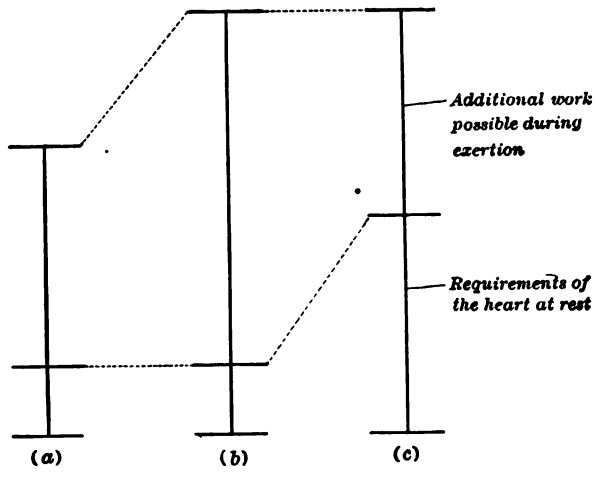

Diagram to represent the three stages of hypertrophy: *a* is a normal heart; *b* is that of an athlete in training; *c* is a heart which has undergone compensatory dilatation and consequent hypertrophy.

Etiology.—1. **From an Interference with the Heart as a Contracting Organ.**—(*a*) *Overexertion* has long been known as a cause of hypertrophy beyond the limits of the normal heart, and is now fully recognized as a very important cause of non-valvular disease of the heart. We have no reason to suppose that in the majority of cases any other factor is concerned than the strain on the heart due to the exertion, although in some cases other factors such as a previous infection or alcohol play a part. It matters not to what class a person belongs, any prolonged or very arduous exertion will sooner or later lead over and above an hypertrophy of work to an hypertrophy which is also associated with compensatory dilatation. We lack sure evidence of the extent to which hypertrophy coming on in foundrymen, hammermen, and others in early middle life is not to some extent due to alcohol or syphilis. The same suspicion can hardly be entertained with regard to the majority of men engaged in college athletic sports, many of whom, from their school-days, have led very careful lives. Even in these, however, we cannot eliminate the effect of a previous infection, an attack of diphtheria or pneu-

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monia, which would detract from the total accommodation power of the heart muscle. Yet, further, certain families are notably long-lived, probably, in chief part, because of particularly good cardiac muscle. Such hereditary endowments, upon whatever they depend, can hardly fail to influence the degree to which muscular work can be pushed without causing hypertrophy. As an example of marked hypertrophy from overexertion the following case may be cited: An undergraduate aged twenty years, while rowing in the summer "eights," "crocked" and was advised not to row any more; he was examined by a London consultant and pronounced to have "two murmurs," according to the patient's account of himself. He was advised to take life easily and avoid any overexertion. About six months later he was seen while suffering from an attack of influenza of a mild gastro-intestinal type, and, being told of his heart condition, the writer examined his heart carefully and could find no sign of any cardiac disease as he lay in bed; his apex beat was well within the nipple line, the sounds were clear, and there was nothing to suggest any abnormality. Seven months later he complained of a feeling of giddiness and some palpitation, coming on at night after playing tennis. In the upright position his apex beat was in the sixth interspace, one-half inch outside the nipple line, fairly localized and forcible; there was pulsation in the fifth space and in the epigastrium. There was no dilatation of or marked pulsation in the veins of the neck. On auscultation, there was a definite systolic murmur at the apex traceable a short distance toward the axilla. The second sound at the apex was reduplicated. At the base there was a well-marked systolic murmur not heard in the vessels of the neck or below the region of the valves. No history of any infection could be elicited, and he was a person of excellent habits of life.

From observation of patients and examination of reports, hypertrophy may affect chiefly the left or the right side, and there are intermediate cases in which both sides are equally affected. Such differences are probably to be attributed to the position of the resistance which is placed in the circulation. If the obstruction is chiefly in the systemic system, caused by contraction of muscles, we would expect the left heart to hypertrophy; if the work required great and prolonged fixation of the walls of the thorax, the obstruction to lung circulation through increased pressure in the alveoli would most affect the right side of the heart.

The following case quoted by Da Costa is a good example of a left-sided hypertrophy following overexertion: The patient was a soldier who suffered from dyspeptic symptoms and constipation, and used tobacco to excess. In 1863 he had severe palpitation which unfitted him for active duty. The heart impulse was wider than normal and the first sound rather weak, but there were no signs of hypertrophy. The condition was regarded as one of irritable heart. In 1870 there was decided hypertrophy. The transverse cardiac dulness was increased, the impulse wide and forcible, and the apex beat lowered. The first sound was prolonged and murmurish. He had some shortness of breath and palpitation, with inability to undergo any great exertion. In another—not so marked—case at postmortem there was hypertrophy of both ventricles and dilatation, the greatest hypertrophy being of the left ventricle.

(*b*) *Hypertrophy as the Result of a Valvular Lesion.*—This is discussed in the articles dealing with the different valvular lesions.

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(*c*) *Hypertrophy from an Obstruction to the Circulation in the Efferent Vessels from the Heart.*—The chamber which pumps blood toward the obstruction tends to be incompletely emptied owing to a diminished onflow in the arteries; the incomplete emptying produces additional stretching of the chamber walls, greater pressure in diastole, and subsequent hypertrophy. The conditions which fall in this section naturally group themselves into those which cause hypertrophy of the right and those which cause hypertrophy of the left side of the heart. Of the former we have emphysema, chronic bronchitis, dilatation of the bronchi, asthma, fibrosis of the lung, lesions of the left side of the heart, and sclerosis of the pulmonary artery. In these conditions a marked epigastric pulsation and an enlargement of the deep dulness well outside the normal limits are of frequent occurrence.

Lichtheim[1] has shown that if the sectional area of the pulmonary circulation be lessened to one-fourth of the normal, hypertrophy of the right ventricle of the heart follows. Hirsch has shown that the degree of hypertrophy in the right heart in emphysema is proportional to the extent of the change in the lungs. The left ventricle under such conditions is either of normal weight or slightly under normal. In pulmonary tuberculosis, even with great fibroid change, hypertrophy of the right ventricle is by no means constant, and when present bears no intimate relation with the degree of lung disease. Hirsch[2] has shown that the hearts of persons dying from pulmonary tuberculosis are smaller than normal; hence the two factors would tend to neutralize one another.

A few cases have been described[3] of right-sided hypertrophy of the heart as a result of sclerosis of the lung arteries. This is frequently present in anthracosis and in those dying in pauper asylums, and is wholly distinct from changes in the lung arteries the result of mitral disease.

With a lesion of the left side of the heart, *e. g.*, mitral regurgitation or mitral stenosis, the left auricle sooner or later is unable to accommodate the extra blood which it receives, the lung system becomes overfull, and this again reacts on the right side of the heart, causing the necessity for greater pressure in order to drive forward the necessary amount of blood; hence the hypertrophy of the right ventricle in cases of chronic mitral disease.

Hypertrophy of the Left Ventricle.—Arteriosclerosis of the systemic arteries has long been known to be associated with hypertrophied heart, but not in all cases does arteriosclerosis even of a marked grade lead to such changes. Affections of two portions of the arterial system are invariably associated with hypertrophy: one is arteriosclerosis of the aorta and the other is arteriosclerosis of the splanchnic vessels. In both these instances the hypertrophy must be looked upon as a direct consequence of the change in the vessels.

The aorta with which hypertrophy is associated is dilated. It has been recently shown by Bittorf[4] and by Strasburger[5] that the elasticity of the aorta in these cases is diminished, *i. e.*, the extensibility is increased; consequently, if a certain volume of blood is propelled into such a vessel it dilates more than the normal, less blood gets to the periphery, the blood

[1] *Die Storungen des Lungenkreislaufs*, Berlin, 1896.
[2] *Arch. f. klin. Med.*, 1899, lxiv, p. 596.
[3] Romberg, *Sclerose der Lungenarterie, Deutsch. Arch. f. klin. Med.*, xlviii, p. 197.
[4] *Münch. med. Woch.*, 1907, xviii.
[5] *Cong. f. inn. Med.*, 1907. Abstract in *Münch. med. Woch.*, 1907, liv, p. 1052.

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pressure is lowered, and reflexly the heart is stimulated and finally becomes hypertrophied. When the aorta has become dilated there is less tendency for it to return to its normal size because of anatomical changes which have taken place in it (formation of fibrous tissue, etc.). Hence, one would now consider the hypertrophy as a compensatory condition to the aortic dilatation, and not *vice versa*. Probably to this cause must be attributed the hypertrophy of the senile heart.

FIG. 8

A is a section of a normal heart; *B* of a heart hypertrophied as the result of renal disease.

Hasenfeld,[1] in a study of 14 cases of hypertrophy from arteriosclerosis, found in all of them a sclerosis either of the aorta above the diaphragm or of the splanchnic vessels. Of these 14 cases 10 were purely arteriosclerotic in nature, while 2 were the result of kidney disease.

[1] *Deutsch. Arch f. klin. Med.*, 1897, lix, p. 193.

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The hypertrophy of the left ventricle, which with such constancy accompanies renal disease of the chronic forms, may in a large number of cases be due to a sclerosis of the splanchnic area, as suggested by Hasenfeld. Such, however, can hardly account for cases of hypertension in renal disease twenty-four hours after the onset and leading to hypertrophy. There is agreement that the hypertrophy of the heart is secondary to the renal disease and is most frequent and most marked in the chronic forms. There are no forms of heart special to particular forms of kidney affection. Sometimes the right ventricle as well as the left is hypertrophied; this is explained as being due to toxæmia or by some as due to the co-existing chronic lung changes, by others as being due to the increased blood pressure in the coronary arteries, and hence the increased nutriment to both chambers.

It is still not possible to decide which of the two rival hypotheses, the mechanical or the chemical, is the correct explanation of the production of hypertrophy. According to the first, known as Traube-Cohnheim's theory, the cutting off of a portion of a capillary system causes a rise in aortic blood pressure. Cushing, for instance, finds that an increase in the pressure in the cranial cavity, until the pial vessels become blanched, causes reflexly a stimulation of the heart until the pressure has risen sufficiently to make the vessels patent again. But against this, excision of one kidney is not always followed by hypertrophy, and tying both renal arteries is not followed by an increase in aortic blood pressure.

The second or chemical hypothesis of Bright, Johnson, Rosenbach, Senator, etc., supposes a failure in the excretion and a stimulation of the heart by the unexcreted material in the blood, either directly or indirectly, by causing contraction of the small bloodvessels. But hypertrophy can occur without a demonstrable excess of urinary constituents in the blood, and the injection of large quantities of urine into animals does not produce any marked effect on the circulation. The viscosity of the blood is not altered to a degree sufficient to account for the hypertrophy.

(*d*) *Mechanical Obstruction to Respiration.*—Any obstruction to the expansion of the chest during respiration will give rise, if long continued, to hypertrophy of the heart; just as fixation of the chest in certain bodily exercises causes some degree of right heart embarrassment, so any obstruction to normal respiratory movement, by causing more force to be expended, gives rise to hypertrophy.

Pleuritic Adhesions.—An association between this and right-sided heart hypertrophy has been noted.[1] There is some other factor, however, causing the hypertrophy, for cases with few or localized adhesions very often give rise to considerable hypertrophy. In some, diaphragmatic adhesions, by which the movements of the diaphragm are impeded, give rise to considerable hypertrophy, yet the amount of hypertrophy from pleuritic adhesions is not in proportion to the extent of the diaphragmatic affection.

Deformities of the chest almost invariably give rise to some hypertrophy of the right heart. It is an hypertrophy of the whole ventricular wall, and not only the conus portion, as has been supposed. No satisfactory explanation has yet been given of the mechanism of this form of hypertrophy; it has probably to do with the interference with lung movements or the anatomical changes consequent upon it. Under this section also comes a

[1] Baumler, *Deutsch. Arch. f. klin. Med.*, 1877, xix, p. 471.

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right-sided hypertrophy, which has been described by MacNaughton[1] in choristers.

(*e*) *From an Interference with the Heart from Without.—Obliteration of the Pericardial Sac.*—Two forms of obliteration from pericarditis must be distinguished: First, the cases in which the two layers of the pericardium are adherent, and, second, when, in addition to the adhesion between the two layers, there is also an extension of the cicatricial tissue to the extra-pericardial tissues, thus anchoring the heart to the neighboring structures. The first type is never associated with cardiac hypertrophy; the second is. The older view, that adhesions between the heart and other resistant structures, such as the sternum, opposed a number of hindrances to the proper contraction of the ventricle and consequent propulsion of blood, has in recent years been doubted. It has been shown, for instance, that the hypertrophy bears no relation to the degree of cicatricial fixation and that the synechiæ may be only slight and yet the hypertrophy may be great. It has been supposed in these cases that the hypertrophy is more probably due to other complications, such as lung changes, valvular changes or arteriosclerosis, than to the pericarditis. It is impossible to say to what degree these objections are valid; certain it is that the contracting bands have some, if not the whole, effect, as witness the good results of setting free the heart from its fixation by surgical measures.

French writers describe a form of enlargement of the heart, probably of the nature of hypertrophy, which is found in patients with large abdominal tumors; the causation is not clear. It may be due to some mechanical embarrassment of the heart, a reflex irritation of the heart from the abdominal sympathetic, or a compression of the great vessels of the abdomen and a compensatory increase in aortic blood pressure, as in one explanation of the hypertrophy of renal disease.

(*f*) *Hypertrophy from Interference with Cardiac Muscle.*—The diseases of cardiac muscle are treated elsewhere and this aspect of hypertrophy therefore need not be considered very fully. The interferences with cardiac muscle giving rise to hypertrophy are degenerations and myocardial changes from coronary artery disease, parasites, and new-growths. Of these myocarditis and coronary artery disease produce by far the greatest hypertrophy. On the other hand, degenerations, such as fatty degeneration, are seldom associated with hypertrophy, and in the published accounts of parasites and new-growths of the heart hypertrophy, was not as a rule evident postmortem; so that the power of most of these causes to produce hypertrophy, except those which are treated of elsewhere, is very small.

2. **Hypertrophy from Stimulation of Nerves.**—From what has been said on the immediate stimulus which causes hypertrophy, it follows that an excessive stimulation of the sympathetic nerves of the heart causing an increased rate and force of the beat will ultimately lead to hypertrophy. One of the most marked examples, as well as one of the most frequent, is that which accompanies Graves' disease, in which the heart is frequently outside the usual limits and the apex beat which lies outside the nipple line is forcible. The sounds likewise are accentuated. We are not in a position to say to what extent a direct chemical stimulation of the muscle fibers by thyroid secretion acts, but pending further knowledge we are justified in including it under this heading.

[1] *Lancet*, 1905, ii, p. 1136.

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The hypertrophy which results from excessive sexual indulgence is probably of this nature. Finally, there are cases in which hypertrophy appears to be due to reflex irritation of the nervous centres of the cardio-accelerated centre. Potain was the first to point out that reflex disturbances, such as dyspnœic attacks, which were the result of chronic dyspepsia or catarrh of the bile passages, produced hypertrophy with enlargement of the right heart. This form is fully discussed by Barré.[1] Potain also drew attention to the hypertrophy which follows lesions of the brachial plexus, neuralgias, neuritides, neurosis, and neuromata, a reflex irritation and increased activity.

3. **From an Abnormal Chemical Stimulus.**—*Alcohol.*—The effects of excessive beer drinking have been sufficiently emphasized by Bauer and Bollinger[2] in their researches on the conditions of the heart in Munich autopsies. While it may be doubted whether the conditions they found were due to the excess of fluid, to the alcohol, or to some other constituent, yet it is the general opinion amongst practitioners that the alcohol alone is the harmful ingredient. Bauer and Bollinger found in some of their cases an interstitial nephritis, but over and above the hypertrophy thus associated there were others whose cause was apparently the excess of stimulating beverages. Hirsch[3] has recently found in all his cases of hypertrophy from beer drinking an interstitial nephritis, which he supposes the true cause.

Recently, Bingel has made observations on the effect of the life of the German student on the heart by means of *x*-ray orthodiagrams. The chief characteristics of life at the university as compared with that at the gymnasium are (1) the consumption of a large amount of alcohol, particularly beer, and especially Munich beer, (2) the great amount of bodily exertion that is performed in the ordinary riding lessons and especially in the fencing exercises, and (3) the good-natured excitement which the social life and the mensur bring, with its antecedent and later pleasures. Having carefully followed twenty students through three semesters by means of orthodiagrams, he finds that there is no change in the heart area as plotted out on the screen. Even if the symptoms of overindulgence show themselves as unpleasant feelings in the heart, pressure and a feeling of constriction in the chest, palpitations, stomach sensations, and weariness after slight bodily exertion, there is no change in the size of the heart. It may be mentioned that Bingel's cases differ much in their average age from those of Bauer and Bollinger; those of the former are at that age when compensation is most speedily and effectively developed, those of the latter at an age when the first degenerations of bodily tissues set in.

Various explanations have been offered for the hypertrophy. The action of the alcohol itself is a doubtful explanation, for on this it is difficult to explain the absence of hypertrophy in persons who frequently drink small quantities of spirits. Moreover, the immunity of the winedrinker is often remarkable. Experimentally, alcohol has no power in animals to produce hypertrophy. It has been attributed, again, to the large quantity of assimilable foodstuffs in Munich beer; but this is improbable, for the reason that only certain persons are attacked. The real cause or causes are therefore

[1] *Rev. de méd.*, Paris, 1883, vol. iii, p. i.
[2] *Festschrift f. Pettenkofer*, München, 1893.
[3] *Deutsch. Arch. f. klin. Med.*, 1900, lxviii, pp. 55 and 338.

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obscure, but we may conclude that there is another factor besides the beer in the presence of arteriosclerosis, chronic nephritis, emphysema, the effects of previous infections, or overexertion.

Tobacco.—The production of hypertrophy by this drug has occasionally been described, but the evidence of such is for the most part clinical. Both dilatation and hypertrophy have been noticed. The symptoms of poisoning are the most prominent thing, and probably a timely stoppage of its use prevents the development of hypertrophy. The symptoms which chiefly attract the patient are palpitations, coming on either at rest or after slight exertion, some hyperpnœa, and occasional pain of an anginoid character.

Morbid Anatomy.—With the features which distinguish the muscle of hearts hypertrophied as the result of a valve lesion, dilatation of a cavity, and so forth, we are familiar. These changes consist in an increase in the volume of each fiber, an increase in the sarcoplasm, a broadening of the fibrillæ, and an increase in size and change in form of the nucleus.

Stadler,[1] from the experimental side, has come to some very definite conclusions on the effect produced in animals as a result of artificially produced aortic insufficiency, tricuspid insufficiency, and aortic stenosis. The changes occur in those parts of the heart on which most stress falls, namely, the right auricle in tricuspid insufficiency, the left ventricle in mitral insufficiency and aortic stenosis. The fibers are markedly increased in thickness; the sarcoplasm is much increased, sometimes to such an extent as completely to isolate the fibers. In longitudinal section the spindle-shaped space which encloses the sarcoplasm is enlarged. An increase in thickness of the fibrils is sometimes obvious, but at other times not so marked, or even at times a lessening in their thickness is evident. Vacuole formation is seldom met with. Many forms of nucleus are found, and the conclusion is therefore in agreement with that which Aschoff makes after an examination of the nuclei of hypertrophied human hearts. A most important feature in these hearts is an increase of connective tissue, showing itself sometimes as a diffuse increase affecting a whole segment of the heart or a smaller area. For instance, in the right auricle, in tricuspid insufficiency, not only are the normal septa thickened, but between the single muscle fibers a more or less broad band of connective tissue has been developed. The connective tissue thus found is quite distinct from that so characteristic of myocarditis which is found in small areas. Stadler considers this increase of connective tissue as a reaction from the overfilling which acts so as to increase the elasticity of the walls of the cavity, *i. e.*, to diminish its distensibility. Opinions are less agreed on the presence of an increase of elastic tissue, some observers having found an increase, others no change. There is frequently an increase in the brown pigment at both poles of the nucleus.

The Nuclei of Heart Muscle in Hypertrophied Hearts.—In the human hearts which have been carefully examined microscopically, different forms of nuclei are met with. In fœtal life and probably chiefly, if not only, at that time, the nucleus is rod-like with flat borders and an oval or round cross-section. This form probably only occurs rarely in adult life. The other forms that are frequently met with are:

1. A nucleus with longitudinal and sometimes transverse ridges, the so-called "Leistenkern" of the German authors; seen in longitudinal section

[1] *Deutsch. Arch. f. klin. Med.*, 1907, xci, p. 98.

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it is striated lengthwise, in cross-section the striations appear as buds on the nuclear margin.

2. A flattened nucleus which may be either oval, ribbon-like with round or square ends, or short with almost parallel sides.

3. A greatly enlarged nucleus, enlarged either lengthwise or by distention, the so-called "Riesenkern."

It is impossible to speak of a normal or ideal nucleus in heart muscle. Even the accounts of normal heart nuclei differ widely. From an examination of normal hearts, Inada, a pupil of Romberg, has shown that various forms belonging roughly to those mentioned are to be found.

Schluter[1] concludes that the different forms of nuclei are found strongly marked in hypertrophied hearts. "The nucleus divides in hypertrophy; it becomes larger and there appear in greater abundance the normal changes in size and form of the muscle nuclei." "That the nucleus grows is natural because its size in hypertrophied hearts is in general in normal proportion to the breadth and length of the fiber, in which sense it is possible to suppose that an excentric position of the nucleus is a loss of proportion between nucleus and bulk of fiber." Aschoff and Tawara[2] conclude: "The so-called "Leistenkern" which Albrecht has pictured in his figure 16 we must take to be normal in part as an hypertrophied form of nucleus, and pending further proof we must look upon nuclei with projections in transverse section as normal, when such are more strongly marked, as hypertrophic nuclear forms.

Albrecht[3] points out that the fibrils of the muscle fibers become smaller in diameter, but at the same time there is an increase in the sarcoplasm of the fibers; this gives a larger space unoccupied by fibrils in the neighborhood of the nucleus whose bed of sarcoplasm is much more evident in hypertrophied than in non-hypertrophied muscle. Aschoff and Tawara, however, point out that although this is undoubtedly present in hypertrophied hearts it is also present in normal hearts, especially in relation with the fibers joining the Purkinje fibers with the ordinary muscle fibers of the heart.

The Increase of Muscle Cells in Hypertrophy.—Such is by no means definitely proved. Zielonko, using frogs and rabbits in whom he made an artificial stenosis of the aorta, found an increase in the fibers of the heart. This agrees with the assertion of Kölliker, Rokitansky, Zenker, and Rindfleisch, who all suppose a splitting of the fibers to form new ones. Tangl, however, using the same method as Zielonko, finds that only in fœtal life and shortly after birth is the muscle increased by splitting. There is an absence of mitoses in artificially hypertrophied hearts, and the number of cells which contain two nuclei is not in excess of the normal.

It is somewhat early to form conclusions on the extent to which in various forms of hypertrophy the muscle fibers increase in size or number. In the physiological form of hypertrophy from work the only available histological evidence points to no alteration in the size or appearance of the fibers; hence we must conclude that the increase in thickness must be due to a larger number of normal muscle fibers being present. To suppose that physiological hypertrophy, the muscle only doing extra work at special times, can be distinguished by the presence of normal muscular fibers, and the

[1] *Die Erlahmung des hypertrophierten Herzmuskels*, Leipsic u. Wien, 1906.
[2] *Grundlagen der Herzschwäche*, Jena, 1906. [3] *Der Herzmuskel*, Berlin, 1903.

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pathological or compensatory hypertrophy, where the muscle constantly does increased work, by an increase in the size of the fiber, alterations in the nucleus, sarcoplasm, etc., is a tempting hypothesis, but one for which, as yet, there is no support.

Symptoms of Compensatory Hypertrophy.—From our definition the presence of hypertrophy in itself cannot give rise to many symptoms because we have excluded all consideration of cardiac failure; nevertheless it will be advisable to mention a few, although it is difficult to say whether they are due to hypertrophy or commencing failure. Pain in the precordial region, usually of a dull type, and even true anginal attacks may occur, especially if the hypertrophy is due to disease of the coronaries or myocardial sclerosis. Various subjective sensations, such as transient giddiness, singing in the ears, or flashes of light before the eyes, may trouble the patient. On exertion, unless in well-compensated hearts with slight lesions, there may be dyspnœa.

Physical Signs of Compensatory Hypertrophy.—The appearance of the patient may present no indication; but if the hypertrophy is due to a constant high arterial pressure there may be a florid appearance and a general fulness of the tissues of the face.

Hypertrophy of the right auricle may show itself by a more vigorous pulsation of the veins in the neck, especially when the patient is in the horizontal position; such may be more evident in a tracing in which the upstroke, due to the auricular contraction, can be definitely fixed. It may be possible by palpation to detect over the third and fourth ribs to the right of the sternum an impulse occurring before that of the ventricle. The contractions of the auricle normally give no sound that is loud enough to be distinguished by the ear, but when the auricle contracts more vigorously, as it does in hypertrophy, it may be possible to hear the auricular contraction either to the right of the sternum or over the pulsating jugular area in the neck.

Hypertrophy of the right ventricle usually shows itself by causing a slight bulging in the costal angle with definite positive pulsation, not negative as may be seen normally along the left costal border. The apex of the heart is often pushed over to the left, sometimes diffuse and never easily localized. The pulsation at the apex is usually enfeebled. The venous pulsation in the neck may be marked and the jugular pulse may be of the ventricular type.[1] Percussion may not give any reliable evidence. The first sound over the tricuspid area is loud and the pulmonary second sound is usually accentuated. The sign of enfeeblement of the right ventricle is hyperpnœa coming on with the least exertion.

Hypertrophy of the left auricle is not easy to diagnose. The apex tracing may show a larger wave than the auricular beat usually gives; it may again produce an audible sound, but this is uncertain, and some authors have claimed that when the left auricle is enlarged, especially in dilatation, there is an increase in the dulness at the left apex. A loud presystolic murmur in mitral stenosis usually means, according to Mackenzie,[2] a vigorously acting left ventricle.

Hypertrophy of the left ventricle presents the least difficulty. On inspection there is a forcible pulsation of the chest, especially of the left side,

[1] Mackenzie, *The Pulse*, London, 1902, p. 95.
[2] *Quarterly Journal of Medicine*, 1907, i, p. 39.

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at each heart beat, and if the patient be young, there may be some bulging of the thorax. The carotids pulsate more markedly than normally, and the apex beat, which may be in the nipple line or farther out in the fifth, sixth, or seventh spaces, is prominent and fairly easily localized. To the hand the apex beat is more forcible than normal and longer in duration. Gibson[1] describes a quivering or "shuddering" sensation which is given to the hand. The first sound at the apex is louder and longer, but with some loss of compensation; the sound may be short and sharp, and at the tricuspid there may be a doubling of the first sound. The aortic second sound is accentuated. The pulse is usually full and strong, or if the tension is high from renal disease, it may be hard between the beats, with strong but not large beats.

In the diagnosis of all forms of cardiac enlargement, the *x*-rays are of great service, and when the heart area can be mapped out accurately on a screen, measurements made and compared with those of the normal, such must be the final appeal in matters of enlargement. But it affords no clue whether the enlargement is due to dilatation or hypertrophy, which must be determined by summing up the evidence from other sources.

The Blood Pressure in Hypertrophy.—In the young athlete with a perfectly balanced circulation, even under considerable stress and with a large store of reserve energy, it is unusual to find a high maximum or minimum blood pressure during rest; in fact, comparing young men of the same age and standing such as one finds at the universities, those who take violent exercise as a rule have at rest blood pressures somewhat lower than those whose pursuits are more sedentary. During exercise the blood pressure rises considerably at first, but later on, with the onset of cutaneous hyperæmia and perspiration, the blood pressure is often found below normal. From what has been previously said it is obvious that athletic young men are those whose hearts have undergone some hypertrophy of a physiological kind through extra work being demanded of their circulatory systems, and we may therefore conclude that such hypertrophy does not lead to any marked alteration in the blood pressure. The immediate cause of the hypertrophy in these cases is probably the increased peripheral resistance during exercise; the heart is then stimulated to further activity and hypertrophies.

The records of the blood pressure in cases where hypertrophy is the result of an abnormal condition are different. The cause here, whether nephritis, a valvular lesion, an overstrain, etc., instead of being intermittent, as in the athlete, is constant, the heart has continually to do more work to overcome the obstacle to the circulation, and as a consequence, if there is good compensation, the blood pressure is continually higher than normal. The records of the blood pressure in renal disease, in arteriosclerosis, and in aortic disease need only be mentioned as examples.

When such an hypertrophied heart begins to fail the blood pressure may fall, but the height of the blood pressure is no evidence of the condition of the patient; for a patient whose blood pressure had dropped to 150 mm. from 200 mm. would be in a much worse plight than one whose blood pressure previously 150 mm. dropped to 120 mm.

[1] *Diseases of the Heart and Aorta*, Edinburgh, 1898, p. 743.

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CHAPTER VI.

INSUFFICIENCY AND DILATATION OF THE HEART.

By ALEXANDER G. GIBSON, M.A., M.B., M.R.C.P.

Theoretical.—Cardiac insufficiency is produced by any interference with the heart as a whole or any of its essential parts, preventing a proper discharge of its functions. Such changes are entirely independent of hypertrophy, though this may occur coincidently; in fact, hypertrophy is the property which combats interference with function, as Fräntzel has said, *hypertrophy is the guarantee of life.* Cardiac failure, therefore, may occur in an hypertrophied or non-hypertrophied heart.

For an adequate knowledge of any condition of cardiac insufficiency it is necessary to know exactly the effect of the particular agent causing the failure on each particular function of cardiac muscle. Much light has been thrown on the conditions of heart action by the application, to the study of the human heart, of the researches of Gaskell and Englemann on the five functions of contractility, excitability, stimulus formation (rhythmicity), conductivity, and tonicity. It is clear that when different agencies act on heart muscle, the interference with these functions is not necessarily the same in all cases, and our knowledge to be adequate should include the effect of the cause on each one of these functions. Moreover, certain parts of the heart itself have particular functions more than other parts, thus rhythmicity is most marked at the mouths of the great veins, and least in the ventricles. Unfortunately, clinical methods are as yet unable to give us definite answers to these questions, but we now know that certain forms of irregularity of heart action are connected with a failure of one or more of these functions. Thus *pulsus alternans* is now associated with a failure in the function of contractility, and many conditions are associated with a loss of conductivity, such as in Stokes-Adams disease, and the irregular pulse of mitral stenosis.[1] The instances in which interference with certain functions can be affirmed with accuracy are chiefly those in which perhaps only one of the functions is affected in a manner sufficiently marked to be obvious to clinical methods. In the great majority of cases of heart failure, however, we are quite in the dark as to the state of the various functions.

So far as can be at present predicted it is possible that cases of sudden cardiac failure may belong to a class in which the functions of contractility, excitability, or rhythmicity may be at fault. For instance, if one considers the sudden death that occurs in cases of aortic disease, it is probably due to a failure of contractility for the time being. Again, the sudden death that occurs in fatty degeneration of the heart is probably of the same nature. Accurate knowledge on these conditions is as yet, however, not forthcoming and such suggestions are merely guesses.

[1] Mackenzie, *Quarterly Journal of Medicine.* Oxford, 1907, i, p. 39.

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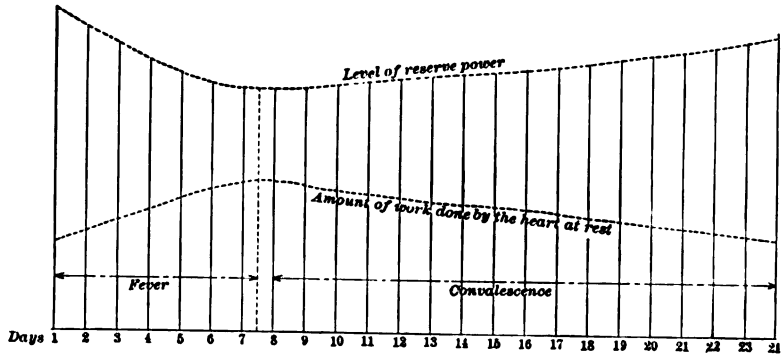
We are better acquainted with conditions of interference with conductivity, because this function, at least in certain parts of the heart, is abnormally developed in certain fibers. In the matter of transference of the stimulus from auricle to ventricle the length of time between the auricular and ven-

FIG. 9


Level of reserve power
Amount of work done by the heart at rest
Fever
Convalescence
Days 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

The diagram represents the conditions of the circulation in an acute fever of six and one-half days' duration. The action of the fever causes changes in the heart muscle so that more work per unit of time is required to keep up the circulation; the same action lessens also the total capacity for extra work.

FIG. 10

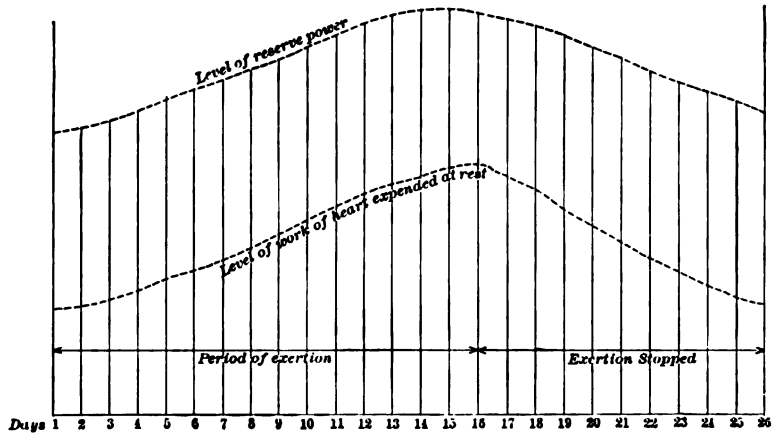

Level of reserve power
Level of work of heart expended at rest
Period of exertion
Exertion Stopped
Days 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26

Diagram illustrating a chronic overstrain with hypertrophy; recovery following stoppage of the overexertion and the hypertrophy disappearing.

tricular impulses, usually one-fifth of a second, serves as a guide to the state of this function. Certain researches suggest that it may be possible to detect alterations in this function, even in the auricles themselves. The stimulus of each contraction begins in all probability in that part which corresponds to the sinus venosus; this stimulus can be transmitted to

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the auricular node either by the auricular muscle or directly by the sino-auricular bundle of muscle fibers; it may therefore be possible in the future to distinguish between several forms of interference with conductivity.[1]

FIG. 11

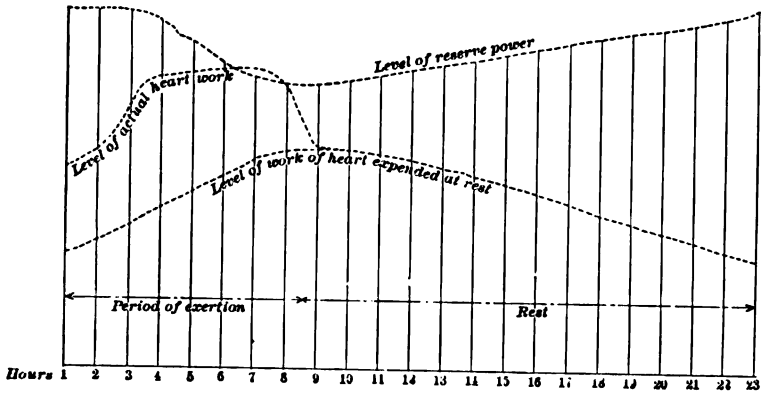
Level of reserve power
Level of actual heart work
Level of work of heart expended at rest
Period of exertion
Rest
Hours 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23

Diagram of the conditions of the circulation in an untrained person undergoing severe exertion. The level of the work required at rest rises, because owing to the increase in pressure in the aorta the cavity of the heart dilates, and with a dilated cavity the total possible work from such a heart diminishes. With rest the dilatation gradually disappears and the conditions return to what they were before the exertion.

FIG. 12

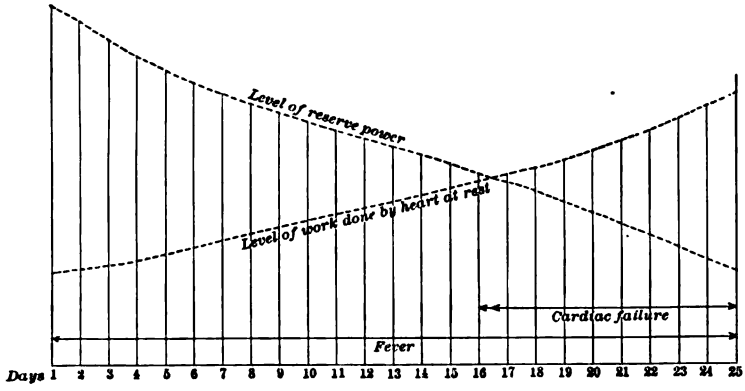
Level of reserve power
Level of work done by heart at rest
Cardiac failure
Fever
Days 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25

Diagram of the conditions of the circulation in a fever, death occurring on the twenty-fifth day from cardiac failure. Symptoms of cardiac failure set in on the sixteenth day of disease.

Mackenzie suggests such a one is the irregularity coming on in mitral stenosis, the dilatation of the auricle being such as to prevent muscular conduction from the great veins to the ventricle, in whose absence the rhythm is taken on by the conducting system nearer the ventricle. Tonicity, again, is a

[1] Keith and Flack, *Journal of Anatomy and Physiology*, 1907, xli, p. 172.

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function which in some cases of cardiac failure is probably one of the chief factors at fault. This, however, will be discussed under Dilatation.

By far the greater number of causes which give rise to cardiac failure are due either to a mechanical interference with the action of the muscle or an anatomical change in the muscle fibers themselves from intoxication, inflammations, etc. In these there is probably an impairment of all functions at the same time, though not necessarily in an equal degree. Under the first class would be included conditions of cardiac failure from valvular defects, overexertion, resistance to the flow of blood in an arterial stem, etc., and under the second the numerous interferences with cardiac muscle such as occur from inflammations, degenerations, parasites, new-growths, etc. A limit should be given to the term cardiac insufficiency for the purposes of description, although of necessity there are no definite lines of demarcation between sound and unsound hearts. A normal heart is one whose reserve power is capable of sustaining a large amount of extra exertion without damage to its structure or size. When any cardiac impairment is present such additional exertion is not possible without distress. The average person who does not take even moderate daily exercise has a lower limit of cardiac endurance than the person who is so accustomed. Another class of patient, even if he walks a yard or two, has breathlessness or some other symptom, but when reclining in bed is comfortable. In the severest type of insufficiency there are symptoms even when at rest, with œdema, orthopnœa, etc., such as are seen in the last stages of chronic heart disease. For clinical purposes such a subdivision as has been indicated is necessary, for it gives at once the lines along which treatment should proceed. Regarded in a slightly different way, these various classes may be looked upon as having different amounts of reserve power; the one in whom symptoms are present only on the severest exertion having the most, another in whom symptoms are present even when at rest having no reserve power at all. This lack of reserve power may be brought about in two distinct ways; in one the requirements of the heart may increase even for the resting condition, such as happens when a valve undergoes increasing erosion, or when, as the result of overexertion, the cavity of the heart dilates; in the second, with a normal amount of work to do, the power of the heart to do that work steadily diminishes; this form occurs in febrile conditions, in inflammations and degenerations of the heart muscle. In practice, probably the two forms frequently occur together, for when a heart is dilated, and the walls stretched, the blood supply is of necessity poorer than if the heart were not subjected to such stress. The foregoing conditions can be shown most clearly by means of diagrams. (See pp. 174 and 175.)

DILATATION OF THE HEART.

Theoretical Considerations.—The term dilatation of the heart is so firmly established, both in the domain of clinical medicine and morbid anatomy, that any description of chronic cardiac failure without a reference to it would be incomplete. So intimately is it associated with certain forms of cardiac insufficiency that the consideration of dilatation of the organ almost usurps that of the other functions. In its clinical sense the term is applied to conditions of heart insufficiency in which the main feature is an enlarge-

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ment of one or more of the cavities of the heart with an enfeeblement of function; in morbid anatomy the term is applied to any enlargement of a heart chamber. The two definitions are by no means co-extensive, for a cavity may be enlarged and yet give rise to no interference with function because a concomitant hypertrophy may be the means of making the organ again effective. Such dilatation would be compensatory, and the term cardiac insufficiency could no longer be applied to it. These cases would come under the pathological variety of hypertrophy which have already been discussed. In the dilatation which is pathological, in that heart failure accompanies it, the cavity of the heart is enlarged to such an extent that the normal pressure per unit area, owing to stretching, cannot be communicated to the heart contents. Such a condition may be the result of two main causes: in the first there is a progressive or sudden dilatation of the cavity by mechanical causes in which the force of the heart remains the same, which, having to act on a greater surface area is not able to give the necessary pressure to the contained blood. This condition, while it leads to stimulation of the heart muscle at first, ultimately produces, either by excessive stretching or by altered nutrition from lack of blood supply, an enfeeblement of the muscle fibers themselves and consequent loss or enfeeblement of their contractile power. The second is that in which, without any alterations in the mechanical conditions, an alteration in the power of resistance or elasticity of the cardiac muscle takes place, by interference either with its nutrition and functions, or the latter alone; the cavity then dilates as a result of the normal pressure exerted on it.

To follow up the mechanical conditions of dilatation a little farther—considering the course of events in a case of mitral regurgitation—the left auricle during systole receives back a certain volume of blood which it had previously given to the ventricle; in addition to this it receives the normal or nearly the normal amount from the pulmonary veins. This extra amount of blood is easily accommodated in the auricle by dilatation from simple stretching. This causes a stimulation of the muscle of its walls and is the stimulus for an increased force being expended at the systole of the auricle, with the result that the ventricle receives the normal amount of blood, together with the extra amount which is thrown back during systole of the ventricle. The circulation is now in a condition of equilibrium again, and supposing that no interference with the nutrition of the heart muscle occurs no loss of balance is likely to occur if the extent of the valve lesion is constant. But supposing the valvular defect increases, the balance between the force necessary to drive the total amount of blood in the auricle into the ventricle and that which it is possible for the auricle even in its stimulated and hypertrophied condition to exert is lost, and the blood accumulates in the auricle and leads to further dilatation. Under these conditions of stretching, it is not possible for the muscle fibers to receive their proper nutriment and a condition of fibrosis results.

The second series of conditions under which dilatation is produced is more obscure—namely, the dilatation that accompanies the degeneration of muscle fibers of the heart. The most marked examples of this are seen in fatty degeneration, and sometimes in the degenerations which accompany fevers. In this class would be included those interferences from inflammation of the muscle—including parasitic irritation—and from new-growths. It would be most rational in this class to suppose that the normal pressure during

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diastole and a lessened resistance to contraction of the muscle produce the same conditions as a heightened diastolic pressure and a greater demand on the contractility of the heart do in the normal condition of the fibers.

So far we have considered dilatation of the heart from increased resistance to contraction, or increased stretching during diastole, and from lesions of the muscle itself; but there is a large class in which the dilatation depends on a direct action on one or more functions of heart muscle acting either in a chemical manner through the blood or through the nerves. Such action, we presume, is not an interference with the muscle cell as a living structure but a pure interference with certain particular functions. The function of heart muscle which in this connection would attract most notice is that of tonicity. Bauer,[1] in 1893, was the first to suggest that certain forms of dilatation were due to a diminution of this function and more recently Herz[2] and Gossage[3] have attributed certain conditions to an interference of the same. We have no method clinically of estimating the condition of tonicity, so that as yet proof of the hypothesis is some way off; yet certain considerations make it very probable that changes in tonicity may be so marked as to produce great interference with heart activity. The heart of *Emys europæa*, or land tortoise, has been shown by Fano to possess in addition to the ordinary rhythmical contractions a slowly developing and slowly subsiding contraction which, when it appears, has the ordinary contractions superimposed on it. This, according to Botazzi, is probably due to rhythmical contractions of sarcoplasm of the muscle fibers; but it may well be objected that while all muscle fibers contains sarcoplasm, only one or two animals in addition to Emys show this phenomenon. But whether it is due to sarcoplasm or not it is probably due to an inherent function of cardiac muscle, most probably tonicity. Again, Ebstein[4] records the observation that stimulation of an exposed non-beating heart with the point of a scalpel was followed by a relaxation of the heart and dilatation of its cavities which was succeeded by an active contraction. Gossage, in speaking of the affection of this function by drugs, considers, probably rightly, that digitalis and antiarin increase tonicity, while lactic acid diminishes it. Supposing tonicity of heart muscle to fail, the heart wall is more flabby than normal and easily receives the inflowing blood during diastole; a normal systole of such a heart will not be sufficient to empty the cavity completely, with more forcible contractions the cavity is emptied as well as before, and the circulation is undisturbed. If from degeneration of the muscle fibers contractility cannot be increased, then there is dilatation and consequent enfeeblement. Supposing contractility alone fails, the pressure in the aorta lessens, and if all the chambers suffer equally, less blood therefore enters the ventricle and the heart merely beats more feebly without undergoing dilatation. If both contractility and tonicity were to fail simultaneously there would be little if any dilatation. In the purely mechanical origin of dilatation, such as occurs from overexertion, both tonicity and contractility oppose themselves to dilatation until from stretching, lack of proper blood or fatigue, tonicity begins to fail. Fatigue of muscle, as is well known, is accompanied by the production of an acid reaction due to sarcolactic acid, which is potent to produce a lack of tonicity.

[1] *Festschrift f. Pettenkofer*, 1893.
[2] *Deutsch. med. Woch.*, 1900, Jahrg. xxvi, 128 and 148.
[3] *Lancet*, 1906, ii, p. 1126.
[4] *Ergebnisse der Physiologie*, 1904, p. 168.

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The Elasticity of Cardiac Muscle.—No data are available bearing directly on this question in relation to cardiac muscle itself. Failing such, we are driven to obtain such evidence as is possible from a consideration of skeletal muscle. It has been shown by Fick and by Donders that the extensibility of muscle (*e. g.*, the additional length that can be added to it) under contraction varies directly with the weight used to stretch it, provided the weights are within the limits which are normal for that muscle. The same is true also of muscle in the resting state, the extensibility being greater than when the muscle is under contraction. Moreover, Fick has shown that the extensibility is not always the same in the contracting state, or as he expresses it, "a muscle is always an elastic structure, but not always the same elastic structure even under the same physiological conditions." The extensibility being greatest in the resting stage, it follows that, other things being the same, the greater danger of dilatation occurs during diastole. What is more important, however, for our purpose is that Weber showed that a muscle in activity could after a certain time be stretched a greater length than the same muscle at rest (Weber's paradox). It has been shown too that muscle, extended while in contraction by a load which gradually increases to a maximum and then diminishes to nothing, does not immediately regain its original length. Both these departures from the normal regular variation of a muscle in length with the weight used to stretch it have now been attributed to fatigue, and if we can apply these facts without risk of error to the pathology of heart muscle, it is evident that in a fatigued muscle we have the most suitable circumstances for the production of dilatation.

The elasticity of cardiac muscle does not depend wholly on muscular tissue, but on elastic tissue and connective tissue which are associated with it. Evidence of the way in which this supporting tissue acts is not forthcoming. The connective tissue in a normal heart is perhaps of too loose a texture to be of use itself in resisting internal pressure, and any stretching of the elastic tissue would be accompanied by a resistance in proportion to the force used. The increase in connective tissue which has been mentioned as being present in compensatory hypertrophy would oppose to the stretching force an increase in cardiac elasticity, and cardiac muscle, not being overstretched, would then be able to work with more efficiency and economy.

Taken in conjunction with what will be said on chronic cardiac failure, it is evident that dilatation of the heart cannot be taken to mean the same as cardiac insufficiency. Dilatation does no doubt accompany many forms of heart failure, but the latter is the important thing and the dilatation is merely a physical sign in the course of the ailment. It is by no means desirable, however, to do away with a term of so much significance in clinical medicine. It would be well perhaps to give a little more exactness to the term, by speaking of cases of cardiac failure with dilatation rather than of dilatation alone.

The accompanying synopsis gives the conditions in which dilatation of the heart is most frequent:

1. From a direct interference with one or more of the primary functions of heart muscle, the function of first importance being that of tonicity.
   - (*a*) From drugs and toxins, tobacco, beer, muscarin, etc.
   - (*b*) From nervous action, *e. g.*, the sudden dilatation from psychical disturbance.
2. Most causes of chronic cardiac insufficiency.

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CARDIAC INSUFFICIENCY.

Acute Cardiac Insufficiency.—Etiology.—(*a*) *Wounds of the Heart.*—These may be direct by a sharp instrument, or indirect from a crush causing a fracture, or from a crush alone. The wound may vary from a large tear opening into one or both ventricles down to an almost microscopic scratch on the surface of the heart. It is not necessary that the wall of the heart should be penetrated. Such cases as show only a very small wound have been examined for the presence of fatty degeneration or other abnormality of cardiac muscle without success. Experiments have been undertaken which show how difficult it is to wound the heart by blows if the pericardium is intact, whether the heart is filled or not. The extent of the rupture is in no sense proportional to the symptoms or the length of time which such a patient survives; small wounds may be fatal in a few hours and with moderately large ones the patient may survive several days. Cases in the literature are by no means rare in which the heart wound has been stitched and the patient recovered. The heart failure caused by wounds cannot wholly be due to mechanical interference with heart action, for the degree of heart failure would then probably show some relation to the size, depth, and position of the wound.

The phenomenon of fibrillation of the heart so frequently observed in experimental animals undoubtedly must occur in human beings, but owing to difficulties in diagnosis we are as yet ignorant of the circumstances under which it occurs. From the analogy of animal experiment we are justified in assuming that fibrillation can occur from electrical, mechanical, and chemical stimulation. Kronecker and Schmey[1] found that by stimulation of the interventricular septum of the dog's heart at the junction between the upper and middle thirds the whole heart could be thrown into fibrillary contractions. They attributed the effect to the destruction of a coördinating centre in the septum. No proof of such a centre has ever been obtained: there is no nervous tissue in that region in greater amount than in other parts, and no stimulation of special portions of the heart where nervous tissue is known to exist or of the entering nerves themselves has been found to cause fibrillation. The two sides of the ventricular septum, as will be described later, are the sites where the two limbs of the bundle of His diverge in their course to supply the muscle of the right and left ventricle. It is questionable whether, from the definite localization of the point according to Kronecker, we are dealing with a lesion of this important part of the cardiac musculature. Electrical, especially faradic stimulation, and chemical stimulation, as, for instance, by perfusing the coronary arteries with a solution of potassium bromide, easily cause fibrillation. The fact that recovery can occur to some extent from all stimuli shows that the hypothesis of the destruction of a coördinating nerve centre is insufficient. Porter[2] has shown that any portion of the heart caused to go into fibrillary contractions can be made to beat in a coördinated rhythmical manner by perfusing the coronary arteries with the animal's blood. Two other conditions, probably alike in their effect on cardiac muscle—namely, tying a

[1] Quoted by MacWilliam, *Journal of Physiology*, Cambridge, 1887, vol. viii, p. 296.
[2] *American Journal of Physiology*, 1898, vol. i, p. 71.

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coronary artery and the injection of suprarenal extract—are potent to cause fibrillation. The relation between fibrillation and the nutrition of the muscle is therefore close, and we may suppose, in the want of further proof, that the mechanical, chemical, and electrical stimuli cause constriction of the coronary arteries supplying special areas. Stimulation of the skin produces in certain persons a local pallor due to vasoconstriction, and the same mechanism may also be present in the cardiac muscle. But as in the skin a stimulus sometimes produces a local vasodilatation not preceded by any vasoconstriction, so there may be such differences in the heart which may explain the inconstancy in the appearance of fibrillation in the heart from certain stimuli, *e. g.*, faradization.

A third danger from heart wounds lies in the amount and rapidity of the accumulation of blood in the pericardium and probably whether such remains in the pericardium or has exit into the pleura. Certain conditions affect the bleeding: a small wound, owing to its position or smallness, may be completely occluded during systole; pressure against the sternum or thoracic wall and quick thrombus formation may limit the hemorrhage. A long period of collapse favors thrombus formation, and anything, such as overexertion, which increases the blood pressure may prove suddenly fatal. The effusion of blood, if its amount does not interfere with the heart's action so as to cause death, and failing an infection from without, undergoes absorption to some extent; an adhesion, either partial or general, of the two layers of the pericardium is then effected.

(*b*) *Spontaneous Rupture.*—The question whether a sound heart ever ruptures must probably be answered in the negative. The more carefully cases of spontaneous rupture of the heart are examined, in a larger proportion definite, although perhaps minute, changes in the muscular wall, which have caused a weakening of resistance at the site of the rupture, are found. The commoner causes of such rupture are infarcts and areas of softening of the heart muscle which are caused by stoppage or partial closure of the coronary arteries, small cicatrices, myocardial abscesses, foreign bodies (needles, etc.), echinococci; localized fatty degeneration, and sclerosis of the coronaries in connection with brown atrophy of the muscle have also been described.

The site of the change, whether inflammation or degeneration, is a weak spot; with the pressure during systole the area becomes stretched and, varying with the elasticity, sooner or later an aneurism appears and finally a rupture occurs. Small aneurisms of apparently little significance can often be seen on the auricles of hearts from old persons; they appear as dilated pouches in between the trabeculæ somewhere near the auricular appendix, and the substance of the dilated portion is apparently only formed of endocardium and epicardium.

As a rule, the site of the rupture is obviously related to some underlying change in the cardiac muscle. The canal leading outward may fork and open into the pericardium by two orifices. The pericardium is usually filled with blood. The condition, according to some recent statistics, occurs most frequently in men between sixty and sixty-five years of age.

Rupture of Valves.—A number of cases of valve rupture, especially of the aortic valves, have been recorded. Such occurs most commonly in valves already slightly damaged by atheroma; and if the valve is more damaged, even slight exertion may bring on rupture in persons so disposed.

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(*c*) *Rapid Effusion of Blood into the Pericardium.*—Cohnheim showed, in 1882, that an injection of oil into the pericardium caused a lowering of arterial blood pressure with an increase of that in the veins. Such fluid in the pericardium acts probably by lessening the capacity of the heart to take in fluid and thus lessens its output.[1]

Three clinical conditions are associated with a rapid effusion of fluid into the pericardium: the bursting of a cardiac aneurism, of an hydatid cyst, or the rapid transfusion of fluid in an acute inflammation. The grade of heart failure bears no marked relation to the amount of fluid; it is more dependent on the rapidity of formation, for with a slowly formed effusion more opportunity is given for the pericardium to relax and the pressure with a given amount of fluid is not therefore so great. Cohnheim found that a pressure of 300 mm. of saturated magnesium sulphate solution could be supported in a dog.

(*d*) *Overexertion.*—To anyone acquainted with some of the severer tests of endurance in athletic contests cases of heart failure are not rare. The story of the messenger from the battlefield of Marathon who fell dead after delivering the news of victory is a good example of a severe case of sudden left heart failure ending in death. In many races men come in pale and perhaps faint immediately after finishing. The failure of heart action affects one or both sides of the heart; if the aortic blood pressure is lowered by feebleness or asystole of the left ventricle, then loss of consciousness or a feeling of dissolution comes on, and if the same happens for the right heart the effect is to cause a great amount of dyspnœa, which is increased by the slightest exertion. Clifford Allbutt's observations on himself are a very good example of this type. The two ventricles may fail simultaneously, with the result that in addition to a feeling of faintness there is also great dyspnœa.

Acute failure may come on during the course of chronic failure or even when all objective signs of failure have disappeared. Two cases reported by Rieder[2] (Case II and Case III) are important in this respect. The first died suddenly after leaving the hospital with no subjective or objective symptoms; the second died suddenly in the course of a chronic heart failure.

(*e*) *The Presence of a Large Amount of Air in the Heart.*—Two sources have probably to be taken into account: First, air which has entered by the veins, and of these the neck veins and the uterine veins after parturition are the most important; secondly, the formation of free gas in the heart during decompression after subjection to high pressures. The first is a danger which has long been taken into account in neck operations, especially in tracheotomy. The patient is in a condition of marked dyspnœa and the inspiratory negative pressure in the neck veins is much greater than during the normal inspiratory phase. Air, when it enters a wounded vein, goes to the right side of the heart, where it hinders the proper onflow of blood into the pulmonary artery. It may occasionally be found on the left side of the heart, having come from the right side through the lung capillaries. Von Jürgenson[3] describes the entry of air into the splenic vein from an ulcer in the stomach. Death occurred in fourteen hours. The pulse was irregular and small; the heart's action was visible, and the contractions very disorderly

[1] See the work of Rehn and of Bode, quoted in Lubarsch and Ostertag's *Ergebnisse der Pathologie*, 1904, p. 852.
[2] *Deutsch. Arch. f. klin. Med.*, 1895, lv, p. 21.
[3] *Ibid.*, 1882, xxxi, p. 441.

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("wirr") and irregular. The face was bloated and œdematous. For the greater part of the time the patient was fully conscious and complained of burning pain in the stomach.

(*f*) *Heart Thrombi.*—The number of cases of heart failure from this cause is extraordinarily small. Pawlowski[1] has collected all the cases recorded and they only come to 25, of which 19 were in the left and 4 in the right ventricle. Such thrombi are frequently of the size of a large walnut and are often attached to some portion of the heart wall or valve; hence the name polypi. They may be the cause of death in persons with no suspected disease or in those suffering from diseases such as typhoid fever.

(*g*) *Sudden Obliteration of a Large Section of the Lung Arteries.*—Experimentally, Lichtheim found that three-quarters of the lung arteries could be tied without producing any lowering effect on the carotid blood pressure. These experiments have been modified somewhat of late. Lichtheim used curarized dogs with opened thorax. If a young dog be used and the left pulmonary artery tied without opening the pleura, the carotid pressure falls, in one case of Landgraf's[2] from 70 mm. to 30 mm. As with all the other causes of heart failure hitherto dealt with, the more sudden the change the greater the failure, and *vice versa*. The symptoms are necessarily those of a right-sided heart failure, marked increased rate of breathing, cyanosis, unconsciousness, etc.

In embolic obliteration of the pulmonary arteries the embolus comes either from the right side of the heart or from a vein. Landgraf describes a case after inflammation of the cæcum and another after endocarditis of the tricuspid valve. The rapidity of death may vary from a few seconds to several days.

(*h*) *Sudden Interference with the Coronary Circulation.*—This is most commonly the result of atheroma, thrombosis, embolism, or a spasm of the muscular walls. Cohnheim showed that after tying a coronary artery that part of the heart supplied by the vessel went into fibrillary contractions. It is doubtful whether a human being could survive such a serious interference with cardiac nutrition, but a gradual obliteration can be sustained. Thrombosis is comparatively rare except as a final stage in angina pectoris. A number of cases of embolism have been described. They are usually the result of atheroma, acute non-malignant endocarditis or malignant endocarditis. The embolism usually affects the right branch of the coronary artery; hence right-sided heart failure is common with cyanosis.[3]

(*i*) *Mechanical Interference with the Heart, e. g., Asphyxia.*—Sudden asphyxia occurs clinically under a number of conditions. It may occur as the result of external interference, such as strangulation, or from an obliteration, partial or complete, within the air passages, such as a foreign body in the pharynx or larynx, sudden œdema of the larynx, sudden œdema of the lungs, or spasm of the bronchial muscular apparatus. The post-mortem appearances are well known; they consist in an enormous engorgement and dilatation of the right side of the heart, especially of the right auricle.

The increase of carbon dioxide in the blood stimulates the cardiac, respiratory, and vasomotor centres in the medulla and the cardio-accelerator centre

[1] Quoted by Thorel, *loc. cit.* [2] *Zeit. f. klin. Med.*, 1892, xx, p. 181.
[3] v. Oestreich, *Deutsch. med. Woch.*, 1896, xxii, p. 148, where the literature previous to that date is given; also v. Barth, *Deutsch. med. Woch.*, 1896, xxii, p. 269.

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in the cord. In the first stages we have, therefore, a slower heart beat, although more forcible from spinal stimulation, a greater respiratory actvity, and an increase in blood pressure. The more forcible inspiration increases the filling of the right heart and lung vessels, and the more forcible expiration increases the venous pressure and the emptying of the left heart. The brunt of the interference tends to fall on the right side of the heart because inspiration tends to fill it and the lung vessels, but expiration tends to empty only the left side and not the right; moreover, the walls of the right auricle and ventricle, being thinner, tend the sooner to yield to the increased internal pressure. During the first stage the most important features are the accelerator action on the heart increasing the force of the beat, the inhibitory action slowing the beat, an increased venous blood pressure, and an increased arterial pressure. During the second stage the inhibitory centre becomes fatigued, the heart is becoming dilated; hence more force is necessary to expel the contained blood; therefore, the accelerator action does not have its proper effect as it does if the right side of the heart is emptied, as can be seen experimentally or clinically when a very cyanotic patient with heart failure is bled. The arterial blood becomes more and more venous, and does not properly nourish the muscle of the walls; hence another source of dilatation is present.

(*j*) *Interference of the Heart from Infections.*—Sudden death is by no means infrequent in the course of some of the severer infectious diseases. Perhaps the one in which it is most frequently seen is diphtheria, but sudden death may also occur in scarlet fever, typhoid fever, pneumonia, smallpox, rheumatic fever, and septicæmia. The explanation is not always easy. In all acute infections there are changes in the heart muscle, usually of the nature of cloudy swelling and sometimes of actual myocarditis, but the myocardial changes seem to be insufficient to account for the sudden death. In diphtheria, again, a parenchymatous change of the nerves and in particular of the vagus has been found.

(*k*) *Poisons.*—In this place may be mentioned the heart failure that comes on as the result of certain drugs, for instance, phosphorus and pilocarpine.

(*l*) *Interference with the Nerves of the Heart.*—The vagus is the nerve by which the functions of the heart are restrained. We are probably justified, in view of recent experiments, especially those of Engelmann,[1] in believing that the vagus contains groups of fibers which act on special functions. Thus, Engelmann has proved that under certain circumstances a pure effect can be obtained on the function of contractility.

We cannot, however, go farther at present than to say that in cases of heart failure from nervous interference it is probably the vagus through which the stimulus is conveyed, and this may have its origin either in the peripheral terminations of the nerve (as with pilocarpine), in the nerve itself, as from a tumor in the neck, in the vagal centre, as in certain cerebral tumors, or at the peripheral end of fibers which convey afferent impulses up to the vagus centre. Probably afferent fibers ending in the vagus centre are supplied to several organs. Injuries to the abdomen frequently produce some heart failure and injuries to the larynx are sometimes fatal. Attention has been called to the sudden death caused occasionally by thoracic

[1] Several recent articles in the *Arch. f. Anat. u. Phys.: Phys. Abt.*

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paracentesis, probably from sudden and severe afferent stimulation of the vagal fibers in the lungs.

Some Types of Sudden Cardiac Insufficiency.—*Sudden Rapidly Fatal Heart Failure from Paracentesis Thoracis.*[1]—A female, aged eight years, had symptoms which pointed to the presence of fluid at the base of the right lung. "On June 14 it was decided to explore the affected area, and an aspirating needle was accordingly inserted in the ninth intercostal space, one and one-half inches from the spine, for a depth of about two inches; no fluid was obtained and only a drop or two of blood. Only one puncture was made, and the whole process took about one minute. A small amount of frothy blood appeared at the mouth and nose. Immediately after the withdrawal of the needle the child was observed to have lost color, or rather to have a livid appearance, with a strong, double-convergent squint, and some rigidity of the arms. The pulse could not be felt and the heart sounds were inaudible. Ether, brandy, and strychnine were injected subcutaneously, and two pints of normal saline were infused into the femoral vein. Breathing continued irregularly for a minute or two, the respirations being slow and gasping, then ceased. Artificial respiration, which was kept up for half an hour, was of no avail, although perhaps for five or six minutes it evoked spontaneous attempts at breathing. The pulse could not be felt after the onset of symptoms." No change was found in the heart at the postmortem examination.

It is not unusual in these cases, if life is prolonged farther than in that quoted, to see convulsions followed by hemiplegia.

Sudden Death from Thrombosis of the Pulmonary Artery.—"Male,[2] aged twenty-four years, with moderately severe attack of typhoid fever. In the middle of the second week a fatal termination occurred under the following circumstances: At the evening visit the patient was quite well, cheerful, and had no pain. The pulse, however, and the apex beat were intermittent without being especially weak; the intermission followed regularly after the second or third pulse beat. The pulse was 80, not reckoning the failure of beats. The patient was quiet until 11 P.M., and slept well. At this hour he awoke, asked for a bedpan, and passed a somewhat profuse, liquid stool without any difficulty. He also took a urine glass and passed fifteen ounces of urine. He had scarcely done this and spoken a few words to his neighbor, when he suddenly made a few strokes with his arms, took a few deep, snorting breaths, and after a few minutes died." A plugging of a main branch of the artery supplying the inferior lobe of the right lung was found.

Right Heart Failure.—Clifford Allbutt relates the following:[3] "In the summer of 1868 I began to walk in the Alps a little too soon for good training. After three days' walking on lower levels, but for longish distances, K. and I crossed the Galenstock, and the next day crossed the Ober Aar Pass. Instead of starting from Grimsel we remained on the Rhone Glacier, crossed the Grimsel Pass from thence, and ascended the Sidelhorn before settling down to the day's work. At the end of the day again, instead

[1] Russell, *St. Thomas' Hospital Reports*, 1899, vol. xxviii, p. 465.
[2] Quoted by v. Jürgenson in Nothnagel's *Specielle Pathologie u. Therapie*, xv, Bd. i, from Virchow.
[3] *St. George's Hospital Reports*, London, 1870, vol. v, p. 29.

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of dropping down on Viesch, we determined to seek the better quarters of the Aeggischhom, and had accordingly to mount that sturdy little Alp by a somewhat rapid ascent. Hitherto I had been in good condition; but the new call for combustion to meet the demand for the additional force required to lift eleven stones and a half to a height of about two thousand feet, threw a great stress upon the right heart. I was suddenly seized with a strange and peculiar *besoin de respirer*, accompanied by a very distressing sense of distention and pulsation in the epigastrium. On placing my hand over my heart I felt a laboring, diffused beat all over the epigastrium. I at once opened my shirt, and ascertained by percussion that the right ventricle was very greatly dilated. I therefore threw myself at length upon the grass, with my shoulders raised, and had the satisfaction in a few minutes of finding the distention, the oppression, and the dulness recede. I was then able to rise and sit down, or even to move about on the level; but, curiously enough, the instant I began to ascend, the symptoms returned. I was therefore obliged to send K. forward and proceed myself with great caution. When I got up to the height of the inn, and had only to walk a mile or two on the level by the waterway, I ceased to suffer, as I felt no general fatigue whatever, and was able to dine well on my arrival. In the night, about 3 A.M., I was suddenly awakened by a severe and distressing palpitation in the epigastrium, with great dyspnœa; there was not, however, the same extension of dulness over the sternum. I went to the window and drew a few long respirations, which gave me ease, and I lost my ailment altogether. No doubt the pressure of a full abdomen against the diaphragm, while recumbent, had again embarrassed the overtaxed right ventricle. Christian Almer, to whom I described my symptoms, said that the same thing had occurred occasionally to himself and to other guides when cutting a number of steps on steep slopes."

Chronic Cardiac Insufficiency.—Etiology.—(*a*) *Lesions of the Heart Muscle.*—These include malnutrition from insufficient or unsuitable food, wasting from new-growth or diabetes; degenerations, such as cloudy swelling, fatty degeneration, amyloid degeneration; the effects produced by infections, such as diphtheria, rheumatic fever, pneumonia, influenza, etc.; new-growths of the heart muscle itself; parasites of the heart, and coronary artery disease.

(*b*) *Lesions of Valves.*—These are described in another section.

(*c*) *Lesions Peripheral to the Heart Itself.*—The causes under this heading group themselves naturally into two, according as the lesion lies in the pulmonary or aortic arterial tree. In dealing with hypertrophy of the heart it was mentioned that a lesion of the lungs causing an obliteration of part of the blood path in the lungs could produce hypertrophy of the right ventricle. Hypertrophy of the right ventricle is the natural reaction to a lesion opposing a proper outflow from the pulmonary artery, but if the limits of hypertrophy have been attained, or if the lesion comes on so suddenly that there is no time for hypertrophy to develop, then the ventricle must become overfilled and the contractions fail. Emphysema, bronchitis, asthma, sclerosis of the lungs, kyphoscoliosis, deformities of the chest, and mitral disease are the most frequent cause of right-heart failure. As in hypertrophy, the left ventricle enlarges from aortic disease, atheroma of the aorta, arteriosclerosis of the smaller vessels, especially in the splanchnic area, and from renal disease; all these conditions may produce cardiac failure sometimes with and sometimes without hypertrophy.

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Hypertrophy of the right ventricle in lung disease may be adequate to carry on the circulation for some time, but when the right heart fails, diminution of the blood flow through the lungs occurs, the blood is insufficiently oxygenated and contains more carbon dioxide than normal, and shortness of breath even at rest comes on. With every additional claim on the heart, especially the slightest exercise, the distress is increased. The feebleness of the right ventricle shows itself in a diminution of the intensity of the pulmonary second sound, cyanosis and overfilling of the systemic veins, enlargement of the liver, albuminuria, and œdema. If compensation is again established, such patients may live a tolerably comfortable life if they avoid exertion of every kind; but the slightest increase in the demands on the right heart may precipitate another attack, and an attack of pneumonia or bronchitis, or indeed any infection, is particularly dangerous. In some cases such a heart insufficiency is brought on without any special antecedent; here it is probable that the balance between hypertrophy and an increasing obstruction in the lung arteries which hitherto has been maintained is now upset by the failure of the hypertrophy.

Emphysema of the lungs, which is preëminently one of the conditions giving rise to this form of cardiac failure, also causes trouble in the left side of the heart. It is difficult to see how such can be accounted for from any effect of the lung condition; it is probably to be sought in the sclerosis of the small systemic arteries, especially those supplying the myocardium, which invariably accompanies emphysema.

The three conditions which affect the left side of the heart chiefly are so similar that they may be taken together—namely, renal disease, particularly the granular, contracted form, arteriosclerosis, especially of the splanchnic vessels, and atheroma of the aorta. All three are associated with a high blood pressure in the stage when hypertrophy is adequate to carry on the circulation. As soon as this fails or some unfavorable condition affects the heart muscle, or an extra amount of exertion requires greater stress, the tension is lowered; the heart beats strongly, but not with its former vigor; the second sound in the aortic area is lessened in intensity; gallop rhythm is present, and the pulse becomes less hard, although probably greater in volume. The face, which previously perhaps was a good color, becomes paler and the patient often complains of drowsiness. With this the urine becomes less in amount; some swelling of the legs, enlargement of the liver, and disturbance of alimentary functions appear.

In the later stages the type of heart failure differs little from that produced by left-sided valvular disease, the diagnosis indeed between the different conditions being extremely difficult.

(*d*) *Interference with the proper movements* of the heart, as in adherent pericardium.

Heart Insufficiency the Result of Goitre.—With any obstruction to the proper air entry and outlet there comes an increased pressure in the lungs during expiration, which is communicated to the blood in the vessels of the lungs, and as a consequence the pressure in the right side of the heart is greater. This leads to hypertrophy and finally to failure of the right heart. In addition to the mechanical changes in the bloodvessels, the increased pressure, as has been determined by postmortem examinations, leads to emphysema of the lungs, which again reacts upon the right heart in the manner previously described. The longer the difficulty of breathing the

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greater the changes. Degenerative processes in the muscle of the right ventricle are usually found, and consist of hypertrophy with fatty degeneration. During life, according to Kraus, these patients belong to two groups: First, those with increased activity of the heart and increased frequency of the pulse, with or without subjective disturbances; secondly, those in whom there has been a longer course, who have an apex beat outside the nipple line and an increase in percussion dulness, especially toward the left.

(*e*) *Excessive Stimulation of the Heart.*—Under this title we include the heart failure from excessive exercise, the rare cases from excessive venery or worry, and perhaps also that occurring in Graves' disease.

We have seen that overexertion is responsible for hypertrophy of the heart and for acute cardiac failure. It is beyond doubt that persons who have to do hard manual labor often suffer from heart failure severer in type and earlier in onset than those who live a more sedentary life. Clifford Allbutt pointed out the frequency of heart failure in the Sheffield foundrymen; workers in the Cornish mines and in the Glasgow shipbuilding yards have been found to suffer in like degree from overstrain. Dwellers in mountainous districts die more frequently from heart disease than those in the lowlands; as an example of these, Münzinger's[1] article on the "Tübingen Heart" may be cited. But the exact value of the factor of overexertion in these cases is more difficult to fix. Not all persons suffer from overexertion even in the areas where heart affections are most common. The patients come from the hospital class, and malnutrition may be a factor. This is especially so in Tübingen, where the diet of the peasants is poor. In highly populated centres the possibility of alcohol and syphilis requires careful elimination. Further, even though the former factors are not valid, a previous infection, such as rheumatic fever (even one of its slighter forms), diphtheria, pneumonia, influenza, or typhoid fever—all have their own effect in interfering with the structure of cardiac muscle at the time, and therefore lessen its reserve power later in life. Proof of the effect of early disease on heart efficiency is not forthcoming, but the tendency of late years has been somewhat to regard the effect of excessive exercise in the production of cardiac failure as less important.

Von Leyden[2] thus classifies the effects of overexertion on the cardiovascular system:

I. (*a*) Atheroma of the aorta.
   (*b*) Arteriosclerosis.
II. Rupture and insufficiency of the aortic valves.
III. Pure cardiac failure (muscular).

Atheroma of the aorta and arteriosclerosis have been previously referred to; we may mention, however, that there is some possibility, from recent researches, that both these conditions may result from the increased aortic and peripheral pressure which occurs during exertion. All drugs which produce an increase in blood pressure produce atheroma of the aorta experimentally and, the more powerful the drug to cause a rise in arterial pressure, the more does it cause changes in the aorta.[3]

Rupture of the aortic valves is a serious condition produced by great

[1] *Deutsch. Arch. f. klin. Med.*, 1877, xix, p. 447.
[2] *Zeit. f. klin. Med.*, 1886, xi, p. 111.
[3] Rickett, *Journal of Pathology and Bacteriology*, 1907, xii, p. 15.

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momentary overexertion. The onset of symptoms is very sudden and the symptoms themselves very alarming; they are those of a very severe aortic insufficiency. Insufficiency of the aortic valves coming on slowly, with progressive enlargement of the heart, is discussed elsewhere.

The effects of exertion on the heart have been studied by means of the *x*-rays. Taking normal, healthy, athletic men, there is agreement that hard exercise for a short time is not productive of any change which can be attributed in any sense to a dilatation of a cavity. Lenhoff and Levy-Dorn[1] examined the hearts of wrestlers before and after wrestling for a period of ten to thirty minutes. They found that to percussion there was a slight increase in the heart area, but by the *x*-rays the whole heart was lowered from descent of the diaphragm, and, apart from a very slight increase in the convexity of the right boundary line of the heart figure, no change could be detected.

In the forms of heart failure, directly the result of overexertion, there are several variations. Such acute attacks may be followed by complete recovery or even with every precaution may develop into a chronic form. In Rieder's case quoted the patient never rose again from his bed and died after two and a half months' illness. The commoner types may be grouped under four headings:

1. Young men accustomed to take violent exertion and engage in competitions frequently seek advice for palpitation, occasional giddiness or faintness, and an earlier onset of dyspnœa when undergoing exertion. The apex is usually well outside the nipple line, the impulse forcible and localized, the first sound is accentuated loud and clear, and the second sound at the aortic area is accentuated; the pulse is large and strong, and the maximum blood pressure is increased.

2. Men of the ages of thirty-five to forty-five years who have for a number of years had laborious work as foundrymen, hammermen, etc., complain of fainting attacks or occasional vomiting and palpitation after exertion. They frequently have well-developed aortic regurgitation, and it is probable that in most cases the primary effect of the exertion has been atheroma of the aorta.

3. A third type occurs in young men of the working class. They complain of general ill-health and inability to do their ordinary work and perhaps some indigestion. They are sometimes mistaken for malingerers. On examination they are, as a rule, pale; the apex is in the nipple line, not easily localized and not forcible. There is marked epigastric pulsation. The area of dulness is increased to the right. The sounds are for the most part clear, but usually there is marked accentuation at the pulmonary aortic area. The pulse is not large or strong.

4. The fourth type is indistinguishable from a severe case of mitral regurgitation; the patient is bluish and dyspnœic; complains of great breathlessness on exertion and swelling of the legs. Such cases are frequently seen among the Tübingen vineyard workers and others whose occupation is very laborious.

The cause of the heart changes in Graves' disease is by no means sure. The capacity of the heart to do work is always more feeble in Graves' disease than in normal persons; any slight exertion causes breathlessness and an

[1] *Deutsch. med. Woch.*, 1906, Jahrg. xxxii, p. 869.

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increase in the rapidity of the pulse. Serious cardiac failure in young subjects is by no means rare; it usually comes on after a period of steady loss in weight and, in fact, a fatal termination to the disease is usually the result of cardiac failure. In the early stages if the patient has been walking about there may be found a slightly displaced apex beat, a sudden impulse, a slight increase of dulness to the left, a slapping first sound at the apex, followed sometimes by a well-marked systolic murmur, an accentuated second sound over the pulmonary area at the base, and a pulse which is large in volume but poor in tension. Later, œdema, dyspnœa, and cyanosis appear with very little increase in the size of the heart. Postmortem, the cavities of the heart are not usually much dilated, the heart muscle is pale and not markedly increased in amount.

Barie[1] describes the reactions of dyspeptic states on the heart, stomach, and biliary tract. They result in a dilatation of the cavities of the right heart, accompanied sometimes by a secondary tricuspid insufficiency with its clinical consequences. The form of attack is usually sudden and sets in with digestion. It is almost certainly nervous in its origin.

(*f*) *The Action of Poisons.*—The action of alcohol on the heart has been mentioned under Hypertrophy. Hypertrophy of the heart is the early stage; the later stage is heart failure with some special features. The heart is affected little by any other beverage than beer. The reason of this is not known; it is put down as being due to the alcohol, but this is not certain. The enormous quantity of fluid taken may be a factor and, again, many who suffer often lead arduous lives.

The cardiac affection usually comes on after the middle period of life has been passed; the patient finds that certain bodily exertions are impossible without a sensation of pressure or pain in the chest. Attacks of cardiac asthma at night may trouble him. On examination the apex beat is outside its normal limits, somewhat feeble and not easily localized. To percussion both ventricles of the heart are enlarged. The first sound is not pure at the apex, and the second over the aortic area is accentuated. The pulse is somewhat feeble, irregular, and easily quickened by exertion on the part of the patient Recovery from such symptoms with treatment is the rule, but usually the patient suffers from further attacks of heart failure, in one of which he dies. The symptoms are those of severe cardiac failure with considerable dilatation of the heart cavities. It is extremely difficult during the cardiac failure to exclude the possibility of renal disease.

The action of tobacco on the heart is usually seen from smoking strong cigars or strong tobacco in short pipes. Palpitation is the first sign and may be present in numbers of smokers without causing them any inconvenience. Attacks of palpitation are not uncommon and may come on without special cause in the night or after exercise, eating, or with excitement. Pain in the region of the heart is a frequent cause for seeking advice. Faintness on exertion is sometimes present. The pulse is usually small, quick, and often irregular. The size of the heart is, as a rule, not altered, but several competent observers have noted a definite increase in size.[2]

Poisoning with tea or coffee seldom causes alarming symptoms. Palpi-

[1] *Rev. de. méd.*, 1883, vol. iii, p. 1.
[2] See Krehl in *Nothnagel's Spec. Path. u. Therap.*, xv, Bd. i, p. 262

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tation is the most frequent symptom, and occasionally apprehension, with pain in the chest.

Morbid Anatomy and Histology.—Pathological anatomy can seldom give an answer to the question whether a heart is insufficient to carry on its work. Many hearts that have not adequately performed their work during life hardly differ from normal hearts. But although we have not learned to recognize the conditions in the heart which give rise to cardiac failure, the anatomical effects in other organs is very striking—the cardiac liver and spleen afford us a sure means of determining death from heart failure. It must be remembered that the reserve power of the heart in a large number of persons is very small, and therefore a very insignificant lesion might produce a great upset in the circulatory balance if the recuperative power were small. Again, conditions of nutrition exercise a marked effect on cardiac as well as skeletal muscle; for instance, old age, anæmia, tuberculosis, and bad hygienic conditions may give rise to lesions recognizable with difficulty.

The hypertrophied heart is not as good as a normal heart. This is a clinical fact about which there can be no two opinions and by an hypertrophied heart we mean one which gives definite signs of enlargement and therefore probably dilatation. Martius[1] has endeavored to explain this by saying that a definite amount of reserve power is at the disposal of the heart, and if more of this is used for ordinary purposes the less there will be for purposes beyond the ordinary. As it stands this can hardly be strictly true, for Romberg and Hasenfeld[2] have shown that a heart hypertrophied as the result of an artificial valvular lesion has practically the same reserve power as a normal heart. This, however, is not the case in valvular lesions in man, especially when there is some considerable hypertrophy, and it must then be supposed either that the limits of the normal working energy expended at rest are much overstepped or that in addition to the valvular defect there are others in the myocardium. In the commonest cause of valvular deficiency, namely, rheumatic fever, this is now highly probable. Aschoff and Tawara have described, in the muscle of such hearts, accumulations of large cells and giant cells, miliary and submiliary in size, in the connective tissue separating the muscle fibers or in the subendocardial tissue; these collections in the few cases examined have been frequently seen partly or wholly destroying the branches of the conducting system of fibers (Purkinje's fibers). They were constant in all the cases of true rheumatic fever examined and frequently also in those not of a certain rheumatic basis.

Much has been done in the way of a systematic search after the anatomical changes which underlie heart failure. The pioneers in this work have been Krehl and Romberg and their pupils of the Leipsic school. Many publications of great value have come from their researches, but it cannot yet be said that there is any unanimity in the opinions. The cases from which these results have been obtained are those dying from various forms of heart failure, especially valvular lesions, chronic hypertrophy from overindulgence in alcohol, renal disease, etc.

Krehl's method of investigation of such hearts has been largely followed by the later workers; it consists in dividing the heart into slices 1 to 1.5 cm. in thickness in a direction at right angles to the long axis, and from each

[1] *Ergebnisse der Pathologie*, 1894. [2] *Arch. f. exp. Path.*, 1897, xxxix, p. 333.

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slice taking a number of portions which are embedded and finally subjected to serial or partially serial section. The following is a short summary of some aspects of the work:

(*a*) *Changes in the Nuclei.*—Several forms of nuclei were mentioned under the microscopic changes of hypertrophy and provisionally attributed to that process; of this, however, there is by no means any unanimity. Starting with the simple oval nucleus seen most typically in fœtal or early life, two nuclei are frequently seen in the same fiber, one above the other in the long axis. There has apparently in this case been a subdivision of the nucleus into two, because occasionally an elongated nucleus is seen with a construction in the middle. Karyokinetic figures are almost universally absent. Other nuclei are enlarged in the longitudinal direction, their ends being either rounded or square and flattened from side to side. Distention may occur, producing large flat nuclei with a slightly thickened edge; the shape may be that of a shield or plate.

The so-called ribbed nucleus (or *Leistenkern*) is very characteristic of these hearts. It is so called because its appearance on the flat shows longitudinal ridges (sometimes also transverse), which on transverse section are seen to be due to outpushing of the nuclear membrane in the longitudinal direction. Nuclei with jagged edges are also met with. These nuclei are found in more or less intact muscle fibers. If, however, the fibers show considerable vacuolization, fatty degeneration, or other form of cell degeneration the nucleus becomes less deeply staining, more homogeneous, the nuclear network disappears and the "*leisten*" or ridges are less distinct, and the flat or band-like nuclei become more round or oval. As was stated in describing the changes under Hypertrophy, it is probable from Aschoff and Tawara's[1] results, and to them may now be added Schlüter's,[2] that the ribbed nucleus is a progressive change probably indicating hypertrophy.

(*b*) *Pigment* cannot be looked upon as forming any indication of the condition of the heart muscle. It is undoubtedly present in large amount in such hearts as those of old persons and those dying from wasting diseases, such as chronic tuberculosis, but the presence of pigment is no indication of the functional well-being of the heart muscle, because it is present at the end of the first year of life in small amount. Aschoff and Tawara consider it of the nature of an excretion or sediment shed from the fiber.

(*c*) *Fatty Change in the Muscle Fibers.*—In almost all hearts in which there has been insufficiency during life, fat is not difficult to demonstrate microscopically. To refer to Schlüter's results, he found fat in the fibers in cases of arteriosclerosis, of valvular disease, of heart failure from nephritis, and in the so-called idiopathic heart hypertrophy from beer-drinking; he failed to demonstrate more than a very small amount in patients dying from lung diseases with heart changes and in kyphoscoliosis. The fat in the fibers in many places was scanty, but in others abundant, and different places in the same heart gave different appearances. The fat lies in droplets between the muscle fibrils, which for the most part do not suffer any alteration in their cross-striation. The nuclei are for the most part normally stained, and there exists no uniformity between the fat content of the cells and the forms of nuclei which they contain.

[1] *Die heutige Lehre von den pathologisch-anatomischen Grundlagen der Herzschwäche*, Jena, 1906.

[2] *Die Erlähmung des hypertrophierten Herzmuskels*, Leipsic, 1906.

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As regards the presence of fat in muscle cells it resolves itself into the question whether it comes from an infiltration or a degeneration. The newer experiments on fatty degeneration show that it probably comes from the blood; that cells have the power of synthesizing again the fat which they have been in contact with and have decomposed; that the presence of fat in a cell almost invariably means that this process is active; but the presence of too great an amount means either that the fat is a storage product or that the corresponding process, splitting up of the fat for purposes of metabolism, is wanting; so that, although fat in itself probably has nothing to do with cell degeneration, it stands as evidence of the same process.

The fatty infiltration in the older sense is a process of a different effect on the heart muscle; here the normal fat in the interstitial tissue of the heart is increased to such an extent that the muscle fibers are pressed upon so that degeneration and absorption ensue. However, a considerable portion of heart muscle remains which is unaffected by the process so that no loss of function occurs for some time. Neither does the fatty infiltration of the fibers themselves, the so-called fatty degeneration of Virchow, seem to have much effect on the heart functions. It has been proved by Hasenfeld and Fenzvessy and confirmed by Pal, that animals poisoned with phosphorus do not suffer any marked lessening of cardiac function even with acute fatty degeneration. The former two authors assert that a causal connection exists between cardiac insufficiency and fatty change, but that the cardiac insufficiency from lack of proper oxygen supply to the muscle fibers is the cause of the fatty infiltration, and not *vice versa*. It has been found, for instance, that an increase in the movement of the heart influences the movement of blood in the heart walls, so that not only does increased nutriment increase the energy, but also increased energy increases the nutriment. In isolated hearts the pulsating heart allows much more blood through its vessels than the motionless heart, even with the same pressure of blood, because every contraction compresses the heart like a sponge. With increased flow of blood the power of the heart increases and with an increased power the blood flow. We can, from these experiments, suppose with considerable certainty that a diminution in heart power will be followed by a diminution in the blood flow and a consequent change in the conditions of the fibers.

(*d*) *Fragmentation.*—We are not in a position to say with certainty whether or not fragmentation of the heart muscle bears a definite relation to heart-failure, but probably it does not. It affects some hearts and not others. Thus, in Schlüter's series of hearts it was present in those from lung diseases and chronic renal disease, but was absent from the other groups, arteriosclerosis and valvular disease, and from idiopathic heart hypertrophy. It is frequently found in acute infections with severe metabolic interference, exophthalmic goitre, tuberculosis, malignant tumors, and progressive anæmia. No clinical picture is associated with the appearance after death. In sections of hearts showing this condition it appears in patches in certain portions, especially near the papillary muscles and in the lower parts of the ventricle. The cells are abruptly broken across, sometimes in the middle near the nuclei, sometimes away from it. The striation of the affected cells is often not good, but presents not infrequently an unchanged appearance. The nuclei are, as a rule, well stained and show no difference from those of normal fibers. As Albrecht[1] asserts, the rupture of the muscle fibers, occurring

[1] *Der Herzmuskel*, Berlin, 1902.

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as it does in isolated patches, must be produced by a force in the neighborhood of the fibers, which force is probably that of the contraction of the muscle fibers themselves during the fibrillation which occurs in the death throes. A. Fränkel[1] tried the crural arteries in dogs and then tetanized their muscles and found rupture of the muscle fibers.

Karcher made researches on rabbits in which he poisoned them with strychnine; various procedures for altering the nutritional conditions of the muscle showed that a condition similar to fragmentation came on. Dunin got fragmentation by leaving hearts to putrefy in water or by keeping portions of muscle in artificial gastric juice at the body temperature.

The following are Aschoff and Tawara's conclusions on fragmentation and the presence of cement lines (*Kittlinie*):

"1. Fragmentation is absent in the newborn, and in young subjects under twenty years of age is seldom seen. It increases in frequency with age, and in older persons is found in two-thirds of all cases.

"2. Similar relations pertain to fragmentation as to the presence of cement lines, which are taken by us in v. Ebner's sense as contraction lines.

"3. With these contraction lines fragmentation has nothing to do directly, but only indirectly.

"4. Together with contraction lines there is developed with increasing age, especially in different diseases and in the dying heart muscle, irregular contraction areas, *i. e.*, areas of greater and lesser density. The areas of greater density regularly surround those places in which the contraction lines lie and are not seldom bordered near the end or quite at the end by a contraction line.

"5. The tears of fragmentation go almost invariably through the areas of lesser density; often at those places where the areas of different density abut on one another, that is to say, near a contraction line, but very seldom through it.

"6. The ultimate cause of fragmentation is unknown. A tearing of the fibers themselves is possible, even probable, but not demonstrable because in the fragmentation areas themselves no such strong contraction phenomena show themselves as in the neighborhood. On that account one must take into consideration also a tearing or breaking of an earlier perishing muscle portion through the contraction or relaxation and elastic recoil of a yet contractile musculature in its primitive form. The appearance of severe fragmentation is produced by the mechanical postmortem effects.

"7. Never has it been possible through postmortem influences to bring forth the appearance of fragmentation in the hearts of young children or young domestic animals that have shown irregular contractions before death.

"8. Fragmentation lies in no certain relation to any form of disease, and signifies no particular form of death of the patient concerned. How far quantitative differences indicate such an opinion must be decided by further accurate research."

(*e*) *Round-celled Accumulations.*—These are of moderately frequent occurrence in hearts from patients dying of chronic heart failure. They appear as accumulations of round cells with relatively large, deeply staining nuclei and little protoplasm, and are situated in places where there is no

[1] *Discussion in Verhand. f. inn. Med.*, quoted by Albrecht, p. 236.

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accompanying increase of connective tissue. It is possible that these appearances are due in large part to the slowing of the blood and lymphatic circulation from enfeebled heart action, for they are generally unaccompanied by other evidence of inflammatory process. If this is the reason for their presence they can have no significance in the production of heart failure, and their disappearance in cases which recover from heart failure is at least probable.

(*f*) *Areas of Connective Tissue.*—Increase of connective tissue, in the sense of a diffuse myocarditis, is rare in these cases of chronic heart failure; usually there is only a slight increase. They appear as small areas showing an increase of connective-tissue cells, spindle-shaped cells, adult connective-tissue cells, and occasionally some round cells. The remains of muscle fibers are occasionally seen among the connective tissue. Round about the area there is usually an increased number of muscle fibers, sometimes smaller than normal, sometimes not, and these again may be in part surrounded by the connective tissue. The vessels of the area, as a rule, show no narrowing of their lumen, being rather wide than constricted. The shape of the area suggests a connection between the connective tissue and a vascular area.

A satisfactory explanation for these appearances is to be found in the slowing of the circulation. It is not due to multiple abscesses, for such in the cases considered are out of the question. Infarcts and coronary sclerosis are equally improbable, at least in the majority, for they are found in the entire absence of these conditions. The slowing of the circulation, however, is a condition known to be present and in other organs it leads to a certain, although slight, increase of connective tissue. Moreover, from the experimental point of view, cutting of the nerves to an area, *e. g.*, the sciatic nerve, is followed by an increased formation of connective-tissue cells and round cells in the muscles affected.

(*g*) *Lesions of Special Muscle Bundles.*—Albrecht, following the idea that heart insufficiency was due to lesions of particular bundles of muscle fibers, has attempted to show, on the basis of anatomical preparations, chiefly from the sheep's heart, that particular bundles of muscle fibers are affected, especially in the left ventricle, one connecting the posterior part of the ventricular septum with the posterior papillary muscle. Albrecht's conclusions have not been confirmed.

(*h*) *The Conducting System of Muscle Fibers.*—Perhaps of greater significance than any publication of recent date, from the point of view of heart failure is that of Tawara,[1] although the application of the facts there made clear has been done as yet in but a few instances. Stanley Kent (1893) and in the same year His described a band of muscle fibers connecting the auricle with the ventricle in the mammalian heart. It is now a matter of common knowledge that a lesion of this bundle in man gives rise to the group of symptoms known as Stokes-Adams disease. Tawara, under the direction of Aschoff, following the methods of the Leipsic school, demonstrated that this bundle began in the neighborhood of the coronary sinus, in muscle fibers which were easily distinguishable from those of the auricular muscle itself. Shortly before entering the fibrous body of the heart the fibers interlace with one another, and here Tawara gives it the name of Knoten. It then pierces the fibrous body of the heart and appears

[1] *Das Reitzleitungssystem des menschlichen Herzens*, Jena, 1906.

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on the top of the muscular septum of the ventricles, where it divides into right and left branches. These branches are subendocardial, the left spreading out into a fan-shaped area on the septal wall of the left ventricle, the right descending in a chink between two muscle columns on the septal wall of the right ventricle, giving off small branches to the neighboring muscle on its course. The ultimate ramifications of the bundle consists of Purkinje fibers, and are found on the surface of the muscle columns and as the false chordæ tendineæ, the whole being a system partly to convey muscular impulses from the auricle to the various parts of the ventricle, and partly in all probability to allow for a re-inception of the rhythm if the normal source should fail; the Purkinje fibers, being more primitive in structure, apparently retain in greater completeness their primitive functions, especially that of rhythmicity.

The right and left limbs of the bundle both convey fibers to the papillary muscles, the median papillary muscle of the right ventricle being supplied by a recurrent branch from the right limb.

The system of fibers thus described can frequently be seen in the ventricles of the human heart as a thin, grayish layer just beneath the endocardium. It is especially clear, when the false chordæ tendineæ are given off, a little higher up than normally and take a longer course to their destination, for then the edge of the bundle is often marked, as it normally is in the calf, by a line of these offshoots from the bundle. In fact, in some hearts one of these branches, especially on the right side, often assumes such proportions as to become a moderator band, and when such occurs the muscular fibers are present as a central cord of Purkinje's fibers surrounded by connective tissue.

More recently still, Keith and Flack have demonstrated that this system of fibers is of even greater significance. They have shown that in mammals, especially the mole, and in man there is a system of fibers at the origin of the great veins whose structure is easily distinguishable both from that of the venous muscle and that of the neighboring heart muscle. This muscular tissue is extremely like that in Tawara's system, and can be traced into the "Knoten" before named as well as in other directions. The muscular tissue at the roots of the veins sends branches to both auricles and the interauricular septum.

We have in this system, therefore, a complete skeleton of undifferentiated muscular tissue, added to which are the more differentiated parts of the heart. It serves the purpose of originating the impulse at the origin of the great veins and of conveying muscular impulses to the various parts of the heart. Aschoff and Tawara emphasize the importance of taking into account this system and its lesions in cases of heart failure. Albrecht certainly had the right notion in his attempt to find lesions of particular bundles of muscle tissue when explaining heart failure, but unfortunately his attempt has not been rewarded by the success that might have been hoped from it. Aschoff and Tawara have shown that in heart failure in acute rheumatic fever many of the lesions invade more especially the sites of the branches of this system. A thorough re-investigation of the subject of the anatomical changes in heart failure based on the present knowledge of this system is much to be desired.

Symptoms of Chronic Cardiac Failure.— (*a*) *Alimentary System.*— The most important are loss of appetite, indigestion, feelings of distention,

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vomiting, pain in the abdomen, flatulence, meteorism, constipation, and hemorrhoids.

Two causes participate in producing these disturbances: First, the relations of the heart and stomach are such that any increase in the size of the stomach would interfere with the contractions of the heart, and at the same time even a moderate distention would interfere with the movements of the diaphragm; second, any failure of the right side of the heart produces an overfilling of the bloodvessels and consequent impairment of the organs of the abdomen. The actual condition of the organs in the latter state is one of œdema and venous congestion; catarrhal processes are present on all free surfaces—stomach, intestines, bile ducts, etc. Loss of appetite and indigestion are frequent signs of heart failure. They may be the first things brought to the patient's notice, and in the later stages, especially those in which the right side of the heart is at fault, they may be distressing, the patient preferring to be without food rather than submit himself to the discomfort attendant upon eating. With the inability of the stomach properly to digest or forward its contents the food undergoes fermentation with the production of gas; when this assumes a certain magnitude the distention impedes both respiration and cardiac action, and distress follows. Relief almost invariably follows copious eructations of the accumulated gas, but this not infrequently is difficult to attain owing to deficient muscular power in the stomach itself and in the abdominal muscles.

Vomiting is not particularly common except under two conditions: it is met with frequently as a sign of heart failure in athletes after a hard race, and, secondly, it is a constant accompaniment of the later stages of any chronic form of heart failure; in the latter it is often a very bad prognostic sign. It is not possible at present to describe the mechanism by which this symptom arises; it seems to be an effect rather of left-sided than of right-sided heart failure, consequently we might attribute it to a deficiency in the blood supply to the medulla and a stimulation of the vomiting centre. This would receive some support from the analogy of the vomiting that occurs in shock, so frequently seen in a surgical casualty room when patients are having superficial wounds dressed. We must not lose sight, however, of the possibility of its also being due to a reflex stimulation of the vomiting centre by means of afferent impulses transmitted up the vagus fibers from the heart or stomach.

Pain in the abdomen may be dull and aching or sharp and lancinating. It may have its origin in the stomach from the condition set up there; it may be due to the distention of the liver and stretching of its capsule; a tender liver in heart disease is of frequent occurrence. On the other hand, it may be due to distention or other conditions in the intestine. It may be caused by an infarct in one of the mesenteric arteries. And last, it may be caused from a condition of angina, the pain being in the heart itself, but referred to the abdomen.

Any accumulation of gas in the intestine adds to the distress of the patient from the same reason as distention of the stomach; hence the necessity of special attention to the bowels. With the diminution in secretory activity there comes also a diminution in motility; hence the constipation, which is often troublesome. On the other hand, the œdema may be great and the irritation increased to such an extent that a condition of diarrhœa is produced. Any condition of back pressure in the portal system acts unfavorably on

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those places where the portal and systemic system communicate; hemorrhoids, therefore, are frequent.

(*b*) *Cardiovascular System.*—Symptoms connected with this—the system that is at fault—are remarkably few. Palpitation is sometimes complained of, especially in those with large hearts. The patient is sometimes aware of a feeling of fulness in the chest, but this again may proceed from the abdominal organs. Pain referred actually to the cardiac region is infrequent; it is usual, of course, in inflammatory conditions of the pericardium, but here it is due undoubtedly to the stimulation of the nerves of the pericardium and not to any heart failure as such. Pain which is referred to other parts of the body such as in the neck, down the arms, etc., is almost invariably anginoid.

(*c*) *Respiratory System.*—Under this heading come hyperpnœa, orthopnœa, and dyspnœa, attacks of dyspnœa—the so-called heart asthma—Cheyne-Stokes respiration, cough, hæmatemesis, and pain.

The various forms of breathlessness seem usually to be connected with a failure of the right side of the heart and are accompanied by some cyanosis. Haldane and Priestley[1] have recently demonstrated that the rate and depth of breathing is regulated by the amount of carbon dioxide which reaches the respiratory centre in a given time, or in other words, if the tension of carbon dioxide in the blood remains the same, the circulation being unaltered, the rate and depth of respiration will not vary. If, by an increase of the percentage of carbon dioxide in the air breathed in, less is able to diffuse out from the blood, there is an immediate change in the amplitude of respiration which is seen to correspond accurately with the tension of carbon dioxide in the alveolar air. The tension of CO_2 in alveolar air rises during exercise owing to an increased amount being set free; consequently an increased ventilation takes place. From these experiments it is natural to conclude that the reason why hyperpnœa and dyspnœa are such common features in heart failure is because of a deficient elimination of carbon dioxide by the lungs, due primarily to a deficiency in the pumping action of the right or the left side of the heart and a slowing of the circulation in the lungs.

It is well to limit the term hyperpnœa to an increase in the rate and depth of respirations, only applying the term dyspnœa to conditions in which there is distinct distress. Orthopnœa is that condition of hyperpnœa in which the patient assumes the upright position of the trunk, any attempt to lie down being immediately followed by an increase in respiratory distress. Its origin has been attributed to the mechanical conditions in the abdomen and neighborhood of the diaphragm. When orthopnœa is present the abdominal organs supplied by the portal vein are distended partly by blood and partly by œdema fluid. The hyperpnœa necessitates the greatest possible movement of the diaphragm and, if the contents of the abdomen are allowed in a small degree to press against it, the force required in order to effect the necessary ventilation of the lungs must be greater. Orthopnœa, as we should expect, is confined to cardiac disease. According to Lazarus Barlow[2] the onset is usually sudden; it is complete from the first; the condition rarely recedes and frequently advances. The angle assumed by the patient is the nearer a right angle the greater the distress. At post-mortem there is a dilatation of the right ventricle in 80 per cent. of the cases.

[1] *Journal of Physiology*, 1905, vol. xxxii, p. 225.
[2] *General Pathology*, London, 2d ed., p. 685.

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Another factor must be taken into account in considering dyspnœa in cardiac disease. v. Basch supposes that, other things being the same, the extensibility of the lungs becomes less in proportion as the pressure of the blood in the capillaries of the lungs becomes greater, that with greater filling of the lung capillaries the lungs become stiffer. This condition he calls "Lungenstarrheit." It hinders both the expansion of the lungs on inspiration and their contraction on expiration. With the same overfilling of the lungs with blood, owing to a straightening out of the capillaries in the walls of the alveoli, there is an enlargement of the cavity of the alveolus which gives rise to an enlargement of the whole lung (Lungenschwellung). Both of these conditions would act so as to require a greater expenditure of muscular force to effect the normal ventilation of the lungs. Although the general truth of the proposition is admitted and has been demonstrated by experiment, there is as yet not evidence enough to assert that under the conditions of congestion of the lungs occurring in heart disease it is present to a degree capable of offering a great hindrance to respiration.

In the sudden attacks of dyspnœa known as cardiac asthma we must look probably to other causes than those just mentioned. The attacks usually come on at night at the same time as some of the paroxysmal neuroses. The onset is sudden, the distress great, and the face is usually pale. These features suggest a nervous element which, in this particular sense, is wanting in the ordinary cardiac dyspnœa. The pulse is rapid, soft, and irregular in force and frequency. This causes an increase of pressure in the pulmonary vessels. François-Franck found that irritation of the heart or aorta produced reflex respiratory phenomena, such as spasm of the larynx and bronchi, which was intensified by the co-existence of a valvular lesion. Cardiac asthma may be the first sign of heart failure to the patient; it may come on after excitement, a meal, the slightest extra exertion, or without any adequate reason. Krehl notes the frequency of cardiac asthma in arteriosclerosis, coronary artery disease and nephritis, and from the features of the attack and the association with cardiac disease supposes that it is due to temporary weakness of the left ventricle and some increase of pressure and loss of velocity of the blood in the lungs.

Cough in cardiac disease occurs first in acute cardiac failure under the same conditions as vomiting in overexertion; in fact, coughing is frequently suggestive of a milder form of cardiac failure, vomiting appearing later and in the severer forms. It may occur in chronic cases probably from failure of the medullary circulation. But by far the most common cause of its appearance is the reflex stimulation of afferent nerves to the respiratory centre in the medulla. Thus, it is present in catarrh or œdema of the bronchi, changes such as œdema, inflammation, or infarct in the lung tissues. Changes in the pleura and accumulation of fluid may produce the same.

Hæmoptysis is a very common symptom in cardiac failure, especially from disease which affects the mitral valve. It may vary from a sudden profuse hemorrhage such as is seen in cases of mitral stenosis to slight streaks of blood in the sputum. When it occurs early in the course of a mitral stenosis it may be looked upon as compensatory and a relief to an overfilled lesser circulation. In the later stages of mitral failure small hemorrhages are frequent. From postmortem records we know that in these cases there is often marked sclerosis of the pulmonary vessels; many of these probably have weakened spots and, with the continuance of the increased pressure,

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give way, causing hemorrhage into the lungs and bronchi; the former probably are the cause of the infarcts so frequently seen in the lungs, and the latter produce a tinge of blood in the expectoration without the clinical signs of an infarct.

(*d*) *Central Nervous System.*—Apart from the symptoms due to gross brain disease, such as embolism, thrombosis, hemorrhage, etc., there are many symptoms whose origin is not clear.

Increase of brain activity, sleeplessness, and mania are not infrequent. Two factors must be thought of: first, lack of nourishment from insufficient filling of capillaries, and, secondly, uræmia. Of uræmia in cardiac disease we know little; it may come on from continual disturbance of the kidney cells from insufficient arterial blood supply, from pressure on the kidneys due to ascites, and possibly from other conditions.

Unconsciousness in heart disease comes on when there is a marked deficiency in the amount of blood that reaches the brain, and in those in whom the deficiency remains death results. It is not always possible to attribute fainting attacks in normal persons to momentary deficiency in heart action; many such may be due to sudden loss of tonus in the splanchnic area, but since we know that a sudden stoppage of the heart can be produced by the action of the vagus nerve it is right to assume that some attacks of fainting are due to lack of proper blood supply to the brain. The same objection cannot hold when the heart itself is at fault. Sudden fainting in fatty degeneration of the heart and in coronary artery disease with a fatal termination is well known. One of the common symptoms of aortic disease, often the one which first comes to the notice of the patient, is fainting. In aortic disease, if a proper supply of blood is to be given to the brain, the minimum blood pressure must be kept above a certain limit. The blood pressure in aortic disease varies between very wide limits; the maximum is frequently great, 150 to 160 mm., and the minimum may be 80 to 90 mm. To prevent lack of cerebral blood it is necessary that this minimum should not be unduly lowered. The pulse in aortic disease is never very rapid and some time is given for reflux of blood from the arterial system back into the heart; this, however, is usually well compensated for by a strong ventricle. But, supposing, as often happens in aortic disease, the pulse intermits or has an extrasystole and a longer interval between two normal beats, the outflow from the aorta into the heart is not adequately checked during the period of the abortive beat and the system becomes abnormally empty.

Stupor and drowsiness are seldom seen except toward the end of life or in very severe cardiac disturbance. Probably the same cause acts here as in unconsciousness, the failure of the left ventricle properly to fill the arterial system; but from its presence in cases in which the right side of the heart is mainly at fault, with great cyanosis and œdema, we must take into account the possibility of its being due to a chronic poisoning by carbon dioxide with which the capillary blood is overcharged.

Epileptiform Convulsions.—The recent attention which has been given to the study of Stokes-Adams disease leaves no doubt that cerebral anæmia can give rise not only to unconsciousness, but also to convulsions simulating those of epilepsy. It has long been known, from the experiments of Kussmaul and Tennier, that on tying one or more of the four arteries supplying the circle of Willis in dogs, epileptiform convulsions invariably appeared. The same experiment has been repeated by Leonard Hill on himself, who

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found that shortly after compressing one common carotid artery he experienced a feeling of numbness on the opposite side of the body followed by a few clonic convulsions. The experiment is brought forward by Leonard Hill to show the lack of communication between the vessels at the base of the brain, but it also proves the connection between cerebral anæmia and epileptiform convulsions. In Stokes-Adams disease there are differences in the onset of the convulsions, but usually, as in the patients described by Webster,[1] in whom the heart would intermit for periods of ten to twenty seconds, the first warning was pallor of the face coincident with a disappearance of the pulse at the wrist; after some fifteen seconds of absence of the pulse spasmodic twitchings of the muscles of the face were observed; as the period increased the spasmodic movements spread first to the muscles of the neck and ultimately to the arms, trunk, and leg. With the more severe attacks there was concomitant squint or conjugate deviation of both eyes to one or other side. The pupils were widely dilated, respiration was noisy, and froth appeared at the mouth. Unconsciousness during the greater part of the period was complete, and with the return of consciousness flushing of the face occurred with the appearance of the pulse at the wrist.

(*e*) *Integumentary System.*—Cyanosis is due to an overabundance of reduced hæmoglobin in the vessels of the skin. It is not necessarily associated with heart disease. Many normal persons continually have blue hands, ears, and cheeks; in these cases local conditions of the circulation are the cause, for it seldom affects the lips. Again, a cyanotic tint can be seen during cold weather in the faces of persons who are much exposed; in them it is due to capillary dilatation and slowing of the circulation. Chronic alcoholics and persons with arteriosclerosis frequently show cyanotic tints in their faces but the cyanosis of cardiac disease is seldom to be mistaken for any of these.

Œdema.—The œdema of cardiac disease is easily recognized; it occurs first in those parts of the body which are most dependent, in the ankles if the patient is out of bed, in the buttocks or calves if the patient is in bed. The skin looks thin and more transparent; if the œdema is great it may be smooth and shiny. Pressure of a finger easily displaces a portion of the fluid and leaves a dimple corresponding to the finger which, after a few minutes, is again filled up. Most patients complain of some pain on pressure over œdematous parts. If the œdema has lasted for a month or two or if the patient has been walking about, the œdema becomes very hard and considerable pressure is necessary to cause pitting of the skin.

Richard Lower, in 1680, first showed the connection of increased pressure in the veins with the production of œdema; he found that œdema of both lower limbs came on as the result of tying the inferior vena cava; on this experiment he explained the pressure of œdema in cardiac disease. There are three possibilities open according to modern views for an explanation of cardiac œdema whose immediate cause is an overfilling of the veins; it may be due to an increase of pressure and filtration of œdema fluid from the vessels from which transudation normally takes place, namely, in the capillaries; it may be due to an alteration in the permeability of the vessel wall, or it may be due to an increased secretory activity on the part of the cells of the capillary walls. Increase of pressure in the capillaries, although

[1] *Glasgow Hospital Reports*, 1900, vol. iii, p. 413.

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it undoubtedly occurs in cardiac disease, is not the immediate factor in its production, for cutting the vasomotor nerves to a limb and stimulating the spinal cord to produce a dilatation of the small arteries and an increase in aortic blood pressure respectively does not result in any œdema of the limb. Again, if the pressure was the immediate cause of the exudation, tying of the veins should in a short time be followed by an increased lymph flow and the appearance of œdema, but these only appear several hours after the increase of pressure.

The factor of importance is the lack of proper nutrition, both liquid and gaseous, to the tissues as well as an interference with the removal of waste products. If hæmostasis is produced in a limb for an hour, by tying a ligature tightly round it, the specific gravity of the venous blood and of the plasma rises and the lymph flow falls; after the removal of the ligature a small increase of venous pressure easily gives rise to œdema of sufficient amount to be recognized by pressure of the finger. The tendency to œdema formation is great if the limb has been rendered anæmic for an hour by means of an Esmarch bandage. These experiments show the importance of the tissues in the formation of cardiac œdema as opposed to the view first enunciated by Ludwig, that it is due exclusively to the conditions of pressure in the capillaries. Whether the œdema formation of cardiac disease is a filtrate or a secretion cannot as yet be decided.

(*f*) *Renal Conditions in Cardiac Disease.*—The features of the urine in cardiac disease are as follows: A great lessening in the total amount excreted, even to a half or less than the amount excreted before on the same intake of fluid; the color becomes darker, with that the concentration is greater and the specific gravity rises; the reaction is usually strongly acid; deposits after standing are very common. The urea reaches about 5 per cent. in the concentrated urine. The urine acid is often in relatively greater amount than under normal circumstances. It has recently been shown[1] that leucin and tyrosin can be found in the urine of cases in which the liver is enlarged from cardiac disease. The inorganic salts are found to vary considerably in amount. A small amount of albumin is usually found (0.05 to 0.2 per cent. by Esbach's method of estimation). A careful examination of the sediment shows that it contains in a large number of cases white blood cells, an occasional red cell, and a few casts, most frequently hyaline, but sometimes granular and even cellular ones are found.

These changes are found only in those cases in which the function of the right side of the heart is at fault, accompanied by congestion in the venous system. It has been proved by Dreser that even when the dilutest urine is secreted the cells of the kidney do an appreciable amount of work in transferring the waste substances in the blood into the tubules of the kidneys, so that with urine of ordinary concentration considerable work has been expended by the kidney. To do this work properly the kidney must be supplied with its normal amount of arterial blood, for if not, the cells form large quantities of sarcolactic acid and undergo changes which are the beginnings of necrosis. The large amount of sarcolactic acid will account for the constant and well-marked acidity of the urine in cardiac patients; the necrotic changes in the cells of the tubules will account for the increase of uric acid and the presence of albumin; it is not so easy to account for the

[1] Dixon Mann, *Quarterly Journal of Medicine*, 1907, p. 25.

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concentration of the urine. It might have been thought that as the kidney partakes in the tendency to become œdematous the urine would have been more dilute, but normally the concentration of the urine seems to be determined on the one hand by conditions of the blood and on the other hand by the conditions of the blood supply. If the sweat glands are excreting vigorously there is in all probability a tendency for the blood to become more concentrated; the urine now contains less water and rises in specific gravity. If, on the other hand, the peripheral arteries are constricted and the blood pressure rises in the internal organs of the body, the kidneys, as, for instance, under the influence of cold, excrete a large amount of dilute urine. We must probably look to the constant loss of the watery constituents of the blood in the form of œdema fluid elsewhere as the reason for the high specific gravity of the urine, for it has been proved that the blood in conditions with œdema is more concentrated. Further, the formation of œdema fluid takes place as a transudate from the veins rather than from the capillaries nearest the arteries which are more concerned in the secretion of urine.

The Blood Pressure in Relation to Cardiac Failure.—The normal adult man at rest has a maximum blood pressure determined by a large armlet with a Riva-Rocci instrument of about 120 mm. Hg. It varies somewhat above and below, perhaps from 110 to 130, but the average is about 120 mm. Estimated by other instruments, such as Gaertner's or v. Basch's, there are constant differences of a few millimeters of mercury, so that the figures taken by means of one instrument cannot be compared with those taken by a different one. By using one instrument the figures obtained from a number of cases can be compared. Women have a slightly lower average blood pressure than men. Alterations occur as the result of bodily activity, psychical disturbances, age, and certain diseases, such as renal disease and arteriosclerosis.

With an exact instrument it was to be hoped that some indication of the state of the heart was to be found in the records of blood pressure. Such a hope has hardly been justified. As Hensen[1] points out, the variations in the blood pressure of normal persons differs greatly, and in heart failure, especially mitral disease, the irregularity of the heart is such that definite figures for the value of the blood pressure cannot be obtained. In most of the published records of blood pressure the maximum is the only one recorded, but when one considers that in a case of irregular heart from mitral failure the summits of the pulse waves on a tracing vary considerably it is obvious that no constant value can be obtained.

It is different, however, if we take the maximum record obtainable. If one is dealing with young adults without evidence of renal disease an estimate of their maximum blood pressure at something less than 125 mm. of mercury with a Riva-Rocci instrument is probably within the limits apart from psychical or other disturbances. If then, taking the highest maximum blood pressure, we find a value of 140 it is clearly abnormal. Katzenstein[2] has called attention to the fact that in early heart failure, such as can be seen in chlorotic girls, the blood pressure is higher than is expected and may be high when the pulse at the wrist is small and feeble. We are probably

[1] *Deutsch. Arch. f. klin. Med.*, 1900, lxvii, p. 512.
[2] *Hypertrophie u. Dilatation*, München.

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justified in taking Katzenstein's explanation that it is an evidence of a compensatory mechanism, probably a peripheral arterial constriction directed toward an adequate upkeep of average blood pressure.

The difficulty of determining by clinical methods the extent to which any given heart can do extra work is a serious deficiency in the matter of forming an opinion for the future guidance of the patient. Some hearts, for instance, although hypertrophied, will show no signs of failure for many years; others again, even though the hypertrophy may only be small and not of long duration, may often show signs of heart failure, sometimes acute in its onset.

It is as yet too early to predict anything about the usefulness of a method recommended by Katzenstein[1] which depends on the reaction of the heart to an increased blood pressure; the maximum blood pressure is determined accurately in the lying-down position, special care being taken to avoid errors due to a change from a previous position. Both femoral arteries are then occluded below Poupart's ligament by firm pressure by means of the middle finger of each hand, the peripheral part of the artery being felt by the third finger to ensure the complete obliteration of the blood stream. Care must be exercised not to cause pain by the pressure and to avoid all psychical disturbance such as is likely to cause an increase in blood pressure. During the compression the maximum blood pressure is again accurately determined by several observations. The compression is now withdrawn and the blood pressure determined again. In a normal person the blood pressure during the compression rises about 10 mm. Hg. and returns to the normal after the release of the compression. The pulse may lessen slightly in frequency, but as a rule does not alter. When there is hypertrophy of the left ventricle the rise of blood pressure is large, sometimes 40 mm. But still, in hearts in which there is no insufficiency the pulse rate varies little. If there is no alteration of blood pressure or a fall with a marked increase in pulse rate, heart insufficiency is present. The observations have been made on patients whose after histories have been studied; it has been found, too, that in the recovery of a patient from a severe fever the indications of heart insufficiency are gradually replaced by a normal reaction. This work has been confirmed by Fritz Levy[2] and by Fellner[3] and Rudinger,[4] but other observers deny the usefulness of the method.

Treatment.—This is discussed in the section on Valvular Diseases.

[1] *Deutsch. med. Woch.*, 1904, Jahrg. xxx, pp. 807 and 845.
[2] *Zeit. f. klin. Med.*, 1906, lx, p. 74.
[3] *Berl. klin. Woch.*, 1907, Jahrg. 44, p. 417.
[4] Hoke and Mende, *Berl. klin. Woch.*, 1907, Jahrg. xliv, p. 304.

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CHAPTER VII.

DISEASES OF THE VALVES OF THE HEART.

By WILLIAM OSLER, M.D., F.R.S.,
AND
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INTRODUCTION.

General Etiology and Morbid Anatomy.—Acquired valvular defects are the sequence of acute endocarditis or the result of a primary fibrosis. In both cases the effect is the same—a deformity, puckering, and adhesion of the valves, leading to insufficiency or stenosis, or to both combined. Chronic disease of the valves of the heart, then, is a question almost exclusively of valvular fibrosis.

In about 50 per cent. of all the cases this sclerosis is a sequence of acute endocarditis. Among 670 cases of chronic heart disease at the Leipsic clinic, 58.5 per cent. followed acute rheumatism (Romberg). Other acute diseases of childhood are responsible for a certain number of cases, while in a not inconsiderable proportion, particularly of mitral cases, no etiological factor can be determined. In the other great group there is a primary degenerative change in the valve of very much the same nature as arteriosclerosis. There is a senile form which follows the ordinary wear and tear of life. All conditions which keep up permanent high tension lead to thickening and puckering of the aortic and mitral segments; while certain poisons, alcohol, tobacco, and syphilis, may cause primary sclerotic changes in the valves, just as they do in the arteries. The morbid anatomy of chronic valvular fibrosis is very characteristic. In the early stages the edges of the valves are a little thickened and may present nodular bodies, the remnants of organized vegetations. In the aortic segments the corpora Arantii enlarge, the edges thicken, the substance of the valve loses its translucency, and along the line of attachment to the aorta there is opaque sclerosis. In the auriculoventricular valves these early changes are seen just within the margin, and here it is not uncommon to find swellings of a grayish red, somewhat infiltrated appearance, almost identical with the similar structures on the intima of the aorta in arteriosclerosis. Even early there may be seen yellow or opaque white subintimal fatty degenerated areas. As the sclerotic changes increase, the fibrous tissue contracts and produces thickening and deformity of the segment, the edges of which become round, curled, and incapable of that delicate apposition necessary for perfect closure. A sigmoid valve, for instance, may be narrowed one-fourth or even one-third across its face, the most extreme grade of insufficiency being induced without any special deformity and without any narrowing of the arterial orifice. In the auriculoventricular segments a simple process of thickening and curling of the edges

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of the valves, inducing a failure to close without forming any obstruction to the normal course of the blood flow, is less common. Still, we meet with instances at the mitral orifice, particularly in children, in which the edges of the valves are curled and thickened, so that there is extreme insufficiency without any material narrowing of the orifice. More frequently, as the disease advances, the chordæ tendineæ become thickened, first at the valvular ends and then along their course. The edges of the valves at their angles are gradually drawn together and there is a narrowing of the orifice, leading in the aorta to more or less stenosis, and in the left auriculo-ventricular orifice—the two sites most frequently involved—to constriction.

Finally, in the sclerotic and necrotic tissues, lime salts are deposited and may even reach the deeper structures of the fibrous rings, so that the entire valve becomes a dense calcareous mass with scarcely a remnant of normal tissue. The chordæ tendineæ may gradually become shortened, greatly thickened, and in extreme cases the papillary muscles are implanted directly upon the sclerotic and deformed valve. The apices of the papillary muscles usually show marked fibroid change.

Incidence of Involvement of the Valves.—In the collected statistics of Parrot the mitral orifice was involved in 621 cases, the aortic in 380, the tricuspid in 46, and the pulmonary in 11.

Mortality.—The death rate in England and Wales from circulatory disease is 1.66 per 1000. In 1905, 242,276 males, 265,454 females died of diseases of the circulatory system. When one considers that a very large proportion of these cases have their origin in rheumatic fever, we see what an important role this disease plays among the acute infections. The larger number of females is probably owing to the fact that rheumatism and chorea are more common among them.

Age Incidence.—Fully one-half of the cases of valvular disease of the heart occur in young persons. Up to the fifth year children are not very liable to valvular disease, but from the fifth to the tenth a great many cases of chorea and the milder types of rheumatism lay the foundation for subsequent sclerotic changes. Doutbless, many cases of mitral disease owe their origin to the slight valvulitis arising in the course of a tonsillitis. Between the tenth and fifteenth years there is an ever-increasing liability. From this time onward the endocarditic valve lesions diminish. During the adult period from the twentieth to the thirtieth year the maximum number of cases of cardiac breakdown occur—37.16 per cent. in Romberg's Leipsic statistics. In the fourth decade a considerable number of the endocarditic cases drop out and the special sclerotic forms begin to appear, more particularly the syphilitic and those associated with the toxic types of sclerosis. Through the fifth, sixth, and seventh decades there is a progressively diminishing incidence. The figures in Romberg's statistics were for the fifth decade, 12.69 per cent.; for the sixth, 9.10 per cent.; for the seventh, 4.33 per cent.; and for the eighth, 1.05 per cent.

Effects of the Valve Lesions.—The general influence on the work of the heart may be briefly stated as follows: The sclerosis induces insufficiency or stenosis, separately or in combination. Narrowing retards the normal outflow; insufficiency permits a certain reflux of blood, with the effect of dilatation of the chamber behind the affected valve. In the former case the chamber has a difficulty in expelling its contents through the narrow orifice; in the latter the chamber is overfilled by blood flowing into it from an improper

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source, as, for instance, in mitral insufficiency, when the left auricle receives a double current from the pulmonary veins and from the left ventricle.

The heart is fully prepared to meet the ordinary grades of dilatation which constantly arise during the extra calls of exertion, when, as in the course of a fever, its muscle has been enfeebled. At the end of a hundred yards' race, a man has his right chambers greatly dilated and his reserve cardiac power worked to its full capacity, but when the exercise is stopped the heart still goes on beating rapidly and forcibly for some time, for the reason that the cavities are dilated and an extra force has to be expended to make the circulation adequate. The extra tension at the beginning of systole being absent, the dilatation diminishes, the activity called forth by extra stretching of the cardiac muscle abates, and the circulation resumes its normal state. Supposing, however, as in valvular disease, the dilatation of a cavity is permanent, then the constant extra stimulation of the heart required to keep the circulation properly maintained calls forth hypertrophy (see article on Hypertrophy) to combat this extra constant demand upon the heart's resources. When the inception of valvular disease is slow, as from sclerotic changes, the increased activity of heart muscle calling forth a gradual hypertrophy is able to avert any lack of compensation until the valvular deficiency oversteps the limits which increased activity and hypertrophy can oppose. On the other hand, if the valvular defect occurs rapidly, then compensation is disturbed in proportion to the magnitude of the deficiency and its rate of onset, and the heart remains uncompensated until hypertrophy has time to develop. To appreciate its nature the process may be graphically shown in the accompanying diagrams, in which the perpendicular lines represent the power of the work of heart. While the muscle in the healthy heart (Fig. 13 *a*) has at its disposal the maximal force, *a c*, it carries on its work under ordinary circumstances (when the body is at rest) with the force *a b;* and *b c* is the reserve by means of which the heart accommodates itself to greater exertion.

With a gross valvular lesion the force needed to do the ordinary work (at rest) becomes very much increased (Fig. 13 *b*). But in spite of this enormous call for force, insufficiency of the heart muscle does not necessarily result, for the working force required is still within the limits of the maximal power of the heart, a_1 b_1 being less than *a c*. The muscle accommodates itself to the new conditions by making its reserve mobile. But this condition could not be permanently maintained, for there is nothing left for emergencies but the small reserve force b_1 *y*. Even when at rest the heart would be using continuously almost its maximal power. Any slight exertion requiring more extra force than that represented by the small value b_1 *y* (say the effort required in walking or on going up stairs) would bring the heart to the limit of its working power and palpitation and dyspnœa would appear. The increased exertion leads now to the putting on of yet more muscle, enabling the heart the better to meet the added calls on its strength, and with this the extreme limit of cardiac action is raised, and instead of this being at *y*, it now reaches c_1, provided there is no interference with the nutrition of the heart muscle.

To what extent the various degress of valvular insufficiency call forth an increase in reserve power is difficult to decide. It is probable that with a slight lesion the limit at first is not beyond what it would be in a similar normal heart under the same conditions, but when the requirements of the heart, with the body at rest, increase so as to approach the limit of the reserve power, we may infer that the total cardiac capacity is increased in proportion,

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because, unless absolute rest of the body, and probably also of mind, is maintained, any movement and any excitement increases the work of the heart and widens the upper limit of cardiac capacity.

The property of the heart whereby at times greater work can be sustained than when the organ is at rest has an important bearing on the course and the treatment of organic lesions. *Per se*, a valvular lesion if slight may affect but little, if at all, the limits to which cardiac action can be pushed; in other words, a person with a well-marked valvular lesion sometimes endures without any outward symptoms of excessive distress the most arduous trials of endurance. This is in agreement with the results of Hasenfeld's experiments, which demonstrate that the limits of cardiac endurance in rabbits with lesions of the aortic valves are hardly if at all lessened as compared with a normal rabbit. But it must not be supposed that a person with valvular disease can undergo with impunity as arduous, continuous exercise as a person with a normal heart. Because, first, the total work required of such a heart at the height of the exertion is far above that asked of the normal heart under similar circumstances; secondly, valvular lesions in man, especially those from rheumatism, hardly ever leave the muscle in the same state as before, so that less work can be got out of it and the inevitable dilatation leads to a yet further increase in the heart's requirements at rest.

For present purposes we may divide the functional capacity of the heart into two parts, first, that which the organ expends when the body is at rest, and, secondly, the reserve, that capacity which enables the heart to overstep and to increase the limits of this activity. This reserve, a function of cardiac muscle alone, is well marked in youth and increased up to adult age and thereafter diminishes; it is also affected by any interference with cardiac muscle, such as infections, intoxications, malnutrition. In all valvular lesions these rest and reserve capacities should receive consideration. In the early periods the heart's work should be well within the rest limit, so as to throw as little strain as possible on the affected valves and allow healing to take place. When this is accomplished, exercise should be so regulated that the reserve is not called upon too suddenly or too freely, while at the same time the limits of cardiac response are gradually widened. If we condemn a person with valvular disease to live always at or about his rest limits, we may tend to retard the growth of his cardiac reserve. On the other hand, it would invite an attack of cardiac failure to ask him to do an arduous piece of work, or if he had to undergo a serious infection. In valvular disease, although an increased amount of work is demanded of the heart, with the body at rest, the full reserve should, if possible—the part from *b* to *c* in the diagram—be developed and maintained in young persons in whom normally these limits are easily extended by daily exercise. There is no reason why a lad with valvular disease should not in a modified degree undergo the same training as a healthy one. In persons who have arrived at an age when cardiac muscle begins to degenerate the greatest care must be taken. In compensated lesions, exercise of the heart, *i. e.*, work over and above the rest limit, is usually beneficial, but a thorough survey of the patient's cardiac condition should be made from time to time, and the effects of this exercise carefully studied. A heart which undergoes increased exertion gets an hypertrophy of work (see section on Hypertrophy), enlarging in all its parts and the weight increasing. But although the cavities enlarge somewhat, they do so probably in some (as yet unknown) proportion to the increase in

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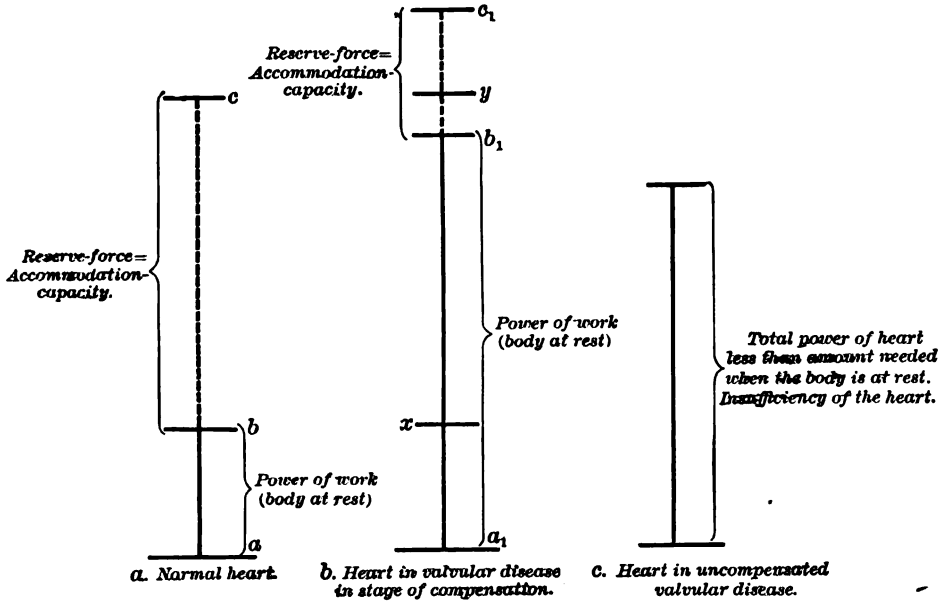
the bulk of the muscle. On the other hand, hypertrophy that follows a valvular deficiency results from the enlargement of a cavity beyond the normal limits to allow of accommodation. The compensation by which an extra amount of blood is forwarded is the expression of the amount of blood in the cavity. Without such hypertrophy the circulation would not be adequately maintained even at rest. The hypertrophy of valvular disease is to be compared accurately with that from overexertion, due in both to a dilatation of one or more cardiac cavities. If a valvular deficiency could be made good, we should expect, as in the treatment of hearts overstrained as the result of exercise, a return of the organ to normal bulk, for no other reason than that the cavity has again resumed its normal, or nearly its normal, size at the beginning of systole.

FIG. 13



(After Martius.)

No doubt the capacity of the heart to hypertrophy in valvular disease is limited by the extent to which the hypertrophy of work can be attained, and such a result in an aged person is not so easily compensated as in a younger one, and the greater the insufficiency the less chance there is to increase the limits of cardiac reserve by hypertrophy.

Turning now to the disturbance of compensation, it is to be borne in mind that any heart, normal or diseased, may become insufficient whenever the call for work exceeds the maximal capacity. The liability to such disturbance will depend, above all, upon the accommodation limits of the heart, the less the width of the latter, the easier will it be to go beyond the heart's efficiency. A comparison of diagrams *a* and *b* (Fig. 13) will immediately make it clear that the heart in valvular disease will much earlier become

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insufficient than the heart of a healthy person. If the heart muscle be compelled to do maximal or nearly maximal work for a long time it becomes exhausted; or, to be more specific, the mechanism by which extra work is called forth from the heart, namely, stimulation of the heart muscle by stretching, and reflexly by the sympathetic nerves from underfilling of the peripheral vessels, fails to act further; the muscle now becomes more stretched, blood supply is interfered with, and the circulation becomes insufficient at that point. In valvular disease, on account of its small amount of reserve force, the heart has to do maximal or nearly maximal work far more frequently than does the normal heart. By stretching of its walls or interference from myocardial degeneration or disease, its power falls below the amount necessary to carry on the work of the heart when the body is at rest, or it may cease to be sufficient even for this. The reserve force gained through the compensatory process may be entirely lost (Fig. 13 *c*). On the

FIG. 14

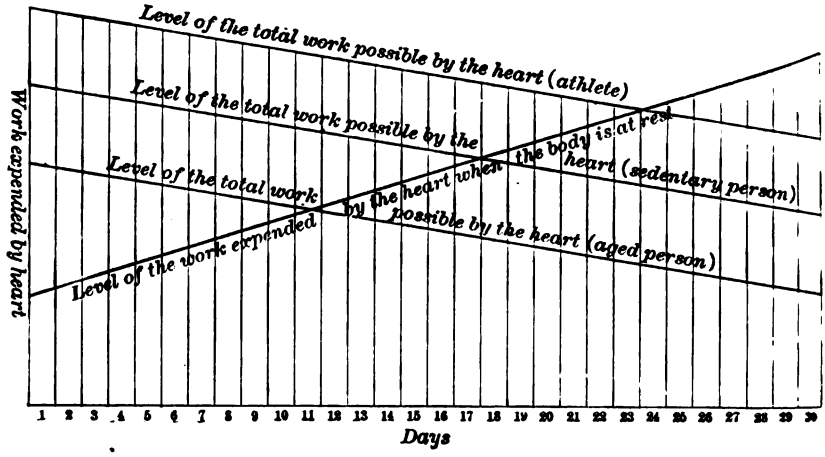
Level of the total work possible by the heart (athlete)
Level of the total work possible by the heart when the body is at rest (sedentary person)
Level of the total work possible by the heart (aged person)
Level of the work expended by the heart
Work expended by heart
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Days

Diagram to illustrate the effects of a gradually increasing valvular lesion with a gradual impairment of the heart muscle, such as probably occurs in malignant endocarditis in persons with different amounts of cardiac reserve. Heart failure occurs when the lines indicating the level of total work cross the line indicating the amount of work required from the heart at rest.

other hand, the insufficiency of the valve at fault may make demands on the heart up to such a point that it approaches and oversteps the upper limit of cardiac accommodation. In the first case, if the loss of reserve force is only temporary, *i. e.*, if the demands on the heart are lessened by rest, or if the muscle can be allowed to recover, the condition is spoken of as a "disturbance of compensation." The term decompensation or "loss of compensation" is reserved for the condition in which the disturbance is permanent. The accompanying diagrams (Figs. 14 and 15) will make clear the foregoing suggestions as to the course of events occurring in valvular lesions.

The schema of Martius (Fig. 16) enables one to understand the relation of the pathological phenomena to the normal cardiac cycle. The contraction of the ventricle takes an appreciable period of time, seven-hundredths of a second (*a*—*b*) to overcome the strong arterial pressure which keeps the aortic (and pulmonary) doors tightly shut. This closure time is the only brief

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period in the cycle in which both the auriculo-ventricular and the semilunar valves are closed, the former as a result of the beginning of the systole, the

FIG. 15

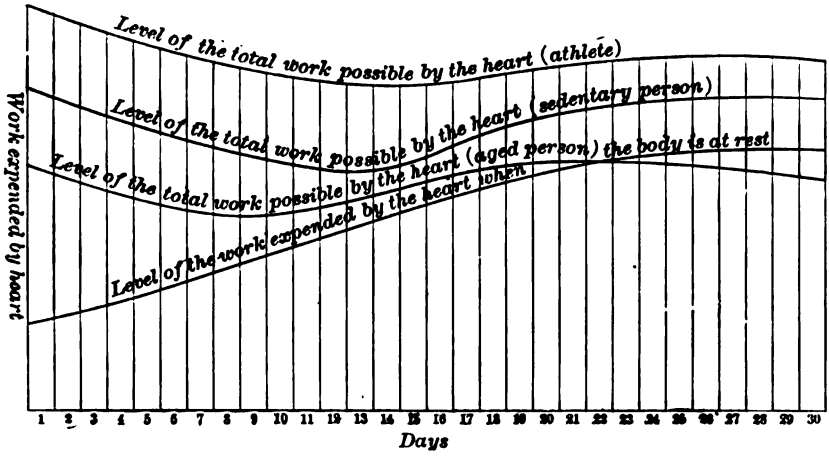
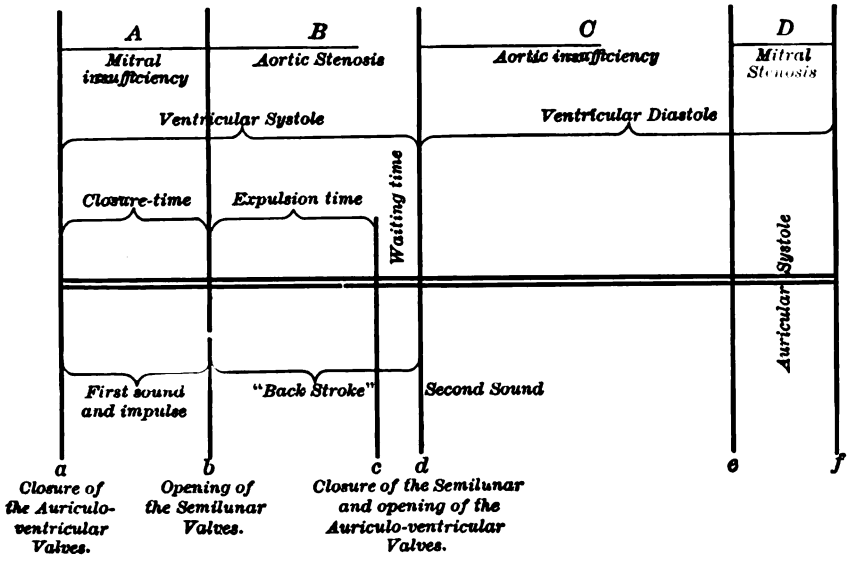

Level of the total work possible by the heart (athlete)
Level of the total work possible by the heart (sedentary person)
Level of the total work possible by the heart (aged person) the body is at rest
Level of the work expended by the heart when
Work expended by heart
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Days

Diagram to illustrate the probable effects of a valve lesion on an athlete, a sedentary person, and an aged person. There is supposed to be a slight early impairment of the cardiac muscle, as is indicated in the descent of the lines indicating the level of total possible heart-work; this is followed by a slight rise which is called forth by the approach of the line indicating the work of the heart at rest. In the aged person the capacity for hypertrophy is least and is not sufficient to oppose the effects of the valvular lesion, and where the two lines cross the heart becomes uncompensated.

FIG. 16



(After Martius.)

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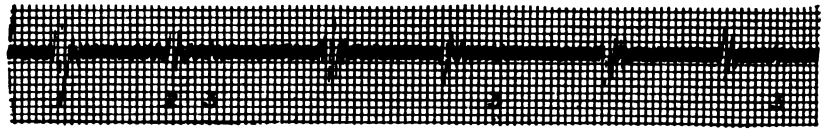
latter until the intraventricular has overcome the aortic pressure. With this closure time correspond the first sound and the heart beat. In the second period of the ventricular systole the blood is driven into the arteries, the expulsion time (*b*—*c*)—and this corresponds with the beginning of the aortic pulse. During this there may be seen at the apex in a forcibly beating heart the "back stroke," as Hope called it. Following the expulsion time there is a brief period—waiting time (*c*—*d*)—before the diastole begins. Clinically the murmur of mitral insufficiency (*a*) coincides, at any rate in its beginning, with closure time, the murmur of aortic stenosis with the expulsion time. The semilunar valves close at the moment when the ventricles begin to relax (*d*), and with this coincides the second sound. Immediately after this the auriculo-ventricular valves open. The murmur of aortic insufficiency (*e*) is heard through the first part of the diastole, sometimes more, while the murmur of mitral stenosis *D* corresponds with the latter part of the diastole of the ventricles and with the systole of the auricles *D*.

In view of the importance for purposes of diagnosis of their proper appreciation, it is necessary from time to time to analyze our views of the heart sounds in the light of recent work. We have long been in the habit of looking upon the normal heart sounds as consisting of two only, a first

FIG. 17



The heart sounds are represented at 1, 2 and 3. (From Einthoven.)

corresponding with and produced by the contraction of the ventricle, and a second sound produced by the tension of the aortic and pulmonary valves. It is probable, however, in view of work by Einthoven[1] and A. G. Gibson,[2] that we must henceforth consider the normal heart sounds as three in number. Gibson, working at the jugular pulse in normal young adults, describes a wave which occurs about half a second after the beginning of the ventricular systole, after the closure of the semilunar valves, and before the auricular contraction. In the cases in which this wave was found it was possible to hear, localized at the apex, a low-pitched clear sound with no harshness or suspicion of a murmur, recalling in type, but not in pitch, the second sound as heard in fat persons. The sound is not easy to hear, and with the most careful attention can only be heard in a proportion of diastolic intervals, the sound being more audible in those cardiac cycles which occur in the interval between expiration and the succeeding inspiration. In striking confirmation of this observation is one of Einthoven's, who has recorded graphically by means of his string galvanometer a third heart sound occurring in a normal young adult without suspicion of cardiac disease. Einthoven's tracings (Fig. 17) bear out Gibson's observation that the sound is not constantly audible, and the amplitude of

[1] *Ein dritter Herzton, Arch. f. ges. Phys.*, Bonn, 1907, cxx, 31.
[2] *Lancet*, London, 1907, ii, 1380.

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the graphic record suggests that, except to skilled ears, the sound is inaudible. The causation of this sound, and probably also of the wave in the jugular pulse, is to be sought in the conditions of the ventricle during the diastolic intervals. On the opening of the auriculo-ventricular valves at the beginning of diastole blood flows into the ventricle from the auricle. After a certain time eddies are formed underneath the valve cusps, and when the ventricle is nearly full they float up sufficiently to close the opening. If, now, this inrush occurs a little more violently than normal, the valves would be closed quickly and some tension put upon them, sufficient probably to give an audible sound. These phenomena may be observed in a sheep's heart by cutting off the auricle and dropping water from a few inches through the auriculo-ventricular opening. The explanation of the sound must, however, be looked upon as hypothetical. That the sound is present can hardly be doubted in view of Einthoven's records, and the necessity for bearing it in mind in the complex conditions of valvular disease is apparent. Clinicians have long been aware of the reduplication of the second sound heard at the apex of the heart only, such, for instance, as in very early mitral disease; and it is probable that this third sound, which we must now consider an integral part of the audible action of the heart, is the same as the so-called reduplicated second sound heard only at the apex. In early mitral stenosis with a slightly increased diastolic pressure in the right ventricle, if the explanation given of this sound is correct, the conditions favorable to the production of such a sound would be increased. Hypothesis should, however, not be pushed farther at present, but it is to be insisted that the normal sound should be taken into account in the diagnosis of early mitral stenosis and probably also in the explanation of all the conditions giving rise to an audible sound in the diastolic period of the heart.

INSUFFICIENCY OF THE AORTIC VALVES.

History.—Cowper,[1] a well-known English anatomist (1666–1709), appears to have been the first to appreciate the significance of insufficiency of the aortic valves. In a paper on "Ossification or Petrification of the Coats of the Arteries, Particularly of the Great Artery," he describes the case of a man, aged thirty years, in whom he found "the valves somewhat thicker and not so pliable as naturally, and did not adequately apply to each other, as in Fig. 4, *a a a*" (referring to an admirable figure of the normal valve closed), "whence it happened sometimes that the blood in the great artery would recoil and interrupt the heart in its systole." The enormous hypertropy and dilatation are described and their significance discussed very intelligently, but he does not describe (as has been stated) the characteristic pulse.

Vieussens, a Montpellier Professor, 1641–1716, whose name is perpetuated in a "valve," published a work on the structure and the causes of the natural movement of the heart (Toulouse, 1715), in which he reported the case of a man, aged thirty-five years, who had violent action of the heart and a pulse that struck the end of the fingers with extraordinary force. He found the left ventricle greatly dilated, the walls hard, and the semilunar valves much diseased, the edges rough and calcified, so that their extremities were not

[1] *Philosophical Transactions*, May, 1705, No. 299.

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able to approach each other and retain in the aorta the blood that had been propelled by the ventricle, so that part of the blood fell back into it.

Hodgkin, the celebrated Guy's Hospital pathologist, in an excellent paper,[1] recognized the importance of what he called *retroversion of the valves of the aorta*. He described very well the characters of the murmur, stating that it was double, continuing in the diastole as well as in the systole, and also the peculiar jerking of the pulse.

In a paper on "Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves,"[2] Corrigan contributed the first really elaborate paper on the subject, and while we must acknowledge that Cowper, Vieussens, and Hodgkin recognized the disease, it is no injustice that the name of the distinguished Dublin physician should be specially connected with it. He thought the condition could be caused by rupture or by curling of the segments or by dilatation of the mouth of the aorta, so that the valves become inadequate. He recognized the double bruit over the aorta and the visible pulsation in the superficial arteries. One of his patients heard this double sound distinctly in his own person, and referred it to a rushing of blood to and from the heart. Corrigan also recognized that certain of the cases were very readily mistaken for aneurism.

Etiology and Morbid Anatomy.—The sigmoid valves guarding the aortic orifice become insufficient under many different conditions, which are important to recognize, particularly as they have a bearing on prognosis.

The frequency of the disease varies in different localities and in different hospitals. Where the patients are from the working classes in large manufacturing centres, and in seaport towns where syphilis prevails, the number of cases is very large. On the other hand, in hospitals with a large proportion of children aortic insufficiency is relatively rare.

One of the most carefully compiled set of figures are those from the Edinburgh Infirmary.[3] Of 2368 cases with cardiac lesions, valvular disease occurred in 80.8 per cent. (1914 cases); 7.3 per cent. of these 1914 cases were aortic insufficiency alone and 17.6 per cent. aortic insufficiency with mitral disease. Barié gives the proportion at 37 per cent. It is the most common form of aortic valvular disease. The ratio between stenosis and insufficiency is very variously given, owing to the fact that the recognition of the former is not nearly so easy, as in many instances the diagnosis of stenosis has rested simply on the presence of a basic systolic murmur. But in hospital practice the senior author would say that aortic insufficiency was ten times as numerous. In his private consultation work in fifteen years the proportion of insufficiency to stenosis cases was 7 to 1.

Age.—It is a comparatively rare affection in childhood, and is most common in men in the fifth and sixth decades. The form following endocarditis occurs at an earlier age, and is met with in children and young adults. A luetic form is met with in comparatively young men. The arteriosclerotic occurs most frequently between the ages of forty and sixty.

At least five groups of cases may be distinguished according to their mode of origin.

1. **Endocarditic.**—The acute infections with which endocarditis is associated attack the aortic and mitral valves with varying frequency. Rheumatic

[1] *London Medical Gazette*, 1829.
[2] *Edinburgh Medical and Surgical Journal*, 1832.
[3] Gillespie, *Edinburgh Hospital Reports*, 1898, vol v. p. 31.

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fever and chorea have a special predilection for the mitral segments. The ordinary septic types attack aortic and mitral valves alike. The severe pneumococcic and gonococcic forms are perhaps seen more frequently on the aortic segments. The ordinary endocarditis of rheumatic fever in children, even when it attacks the aortic valves, does not, as a rule, leave them incompetent. The chaplets of little vegetations may disappear without leaving much, if any, damage. In other cases the edge of one or of two valves is thickened, slightly curled, so that they do not come into close apposition during diastole, and in consequence there is a slight leak. In yet a third group of cases endocarditis has been more severe. The substance of the valve itself has been involved. The segments become adherent, calcification takes place in the hyaline and necrotic tissue, so that the aortic orifice is itself narrowed and there is a combination of stenosis and insufficiency. Sometimes, as a result of the endocarditis, one valve only is affected and a rigid calcified spur remains which prevents the proper closure of the valve. The distinguishing features of the endocarditis group are: the earlier age, the absence of involvement of the root of the aorta so that the coronary arteries are unimpaired, and the greater frequency of the combination of narrowing with stenosis, particularly in young persons. There is a very acute endocarditic aortic insufficiency coming on in the course of a severe rheumatic endocarditis or in the ulcerative forms in septicæmia, pneumonia, and gonorrhœa. Within a week, even within three or four days, the signs of aortic insufficiency may be well marked. In the rheumatic cases recovery may take place, but in the septic forms a malignant endocarditis is apt to develop.

2. **Arteriosclerotic.**—In this, by far the most important form, the insufficiency is part of a widespread arteriosclerosis or of a lesion limited to the root of the aorta. The segments really behave as portions of the aorta, and are involved with it in the degenerative changes. After forty, the aortic segments always show slight signs of wear and tear, and in hard drinkers and hard workers with arteriosclerosis the segments become involved also. The exceedingly delicate texture is lost, the edges curl, and the segments thicken, become foreshortened and so unable to come into close apposition during diastole. So slight is the alteration in some cases that the valves look almost normal, or there may be shortening of only one segment. The surface of the valves may be perfectly smooth, without calcifications or adhesions between the segment, so that there is no narrowing of the orifice. There has been in the valve a simple progressive sclerosis. With this a varying degree of involvement of the arch of the aorta and of the vessels generally is associated; sometimes the arch is in an advanced state of endarteritis deformans, greatly dilated, and even aneurismal. But in other instances the valves themselves show relatively more disease than the aorta. The orifices of the coronary arteries are involved, usually narrowed by the endarteritis, or the branches of the vessels themselves may be diseased. This is the common type met with in hardworking men between forty and sixty in whom there has been no history of rheumatism but the common factors responsible for arteriosclerosis.

Two other varieties may be placed in this category. The luetic form of aortic insufficiency occurs in young men usually within two or three years from the date of infection. It is associated with a syphilitic mesarteritis of the root of the aorta, which may directly implicate the adjoining segments.

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It comes on with severe pain, frequently anginal in character. The insufficiency gradually develops under observation. Sudden death may occur from the involvement of the coronary arteries. In other instances, with appropriate treatment, the condition improves and the case finally settles into one of chronic aortic insufficiency. A parasyphilitic variety is seen in connection with locomotor ataxia. This is probably a degenerative form due to the slow action of toxins, but it may occur in the tabes in comparatively young men who have no widespread arterial degeneration. A senile type of aortic insufficiency is not very infrequent. Met with in men over seventy it is due to a gradual thickening, calcification, and adhesion between the segments, so that there is narrowing of the orifice and slight permanent insufficiency.

3. **Relative Insufficiency.**—Corrigan recognized this in his original paper, and stated that without any organic lesion of the segments, insufficiency might be caused by dilatation of the aortic orifice. Discussion has taken place as to the existence of this form. While rare, there can be no question of its occurrence. Beneke showed that the circumference of the aortic orifice and the aorta just above it increase slightly as age advances, no doubt owing to loss of the elasticity. The cases of this variety have marked dilatation of the aorta, often with extreme endarteritis deformans, and the sigmoid valves a little thickened at the corpora Arantii and along the free border, but without reduction of the closure surface of the valve.

4. **Rupture of the Valve.**—This accident rarely happens to a healthy valve, but it has been quite frequently met with in disease following the strain of a sudden exertion upon segments already diseased or the seat of endocarditis. Still more often it has followed a trauma, a kick from a horse on the chest, or a fall. One or two valves may be involved. It is more frequent in the aortic than in the other valves. Of 72 observations collected by Dreyfus, 46 were of the aortic segments.

5. **Aortic Insufficiency.**—A considerable number of cases of aortic insufficiency are due to congenital malformation of the segments resulting in a fusion of two of the cusps, and almost invariably those behind which the coronary arteries are given off. By no means an infrequent condition, of 17 cases, all of which presented sclerotic changes, the majority had had during life the clinical features of chronic heart disease. The cases are not always congenital, and the mode of production has been discussed by Dr. Maude Abbott in the section on Congenital Diseases of the Heart.

Pathological Physiology.—The prevalent views of the condition of the heart and bloodvessels in aortic regurgitation require some modification. It is commonly held that with a defect in the valves a large amount of blood flows back into the ventricle from the aorta, and that the distention thus produced in diastole has a greater tendency than normal to distend the chamber. But Stewart[1] has shown that the quantity regurgitated, except in very marked degrees of the condition, is not more than a small fraction of the total amount of blood in the ventricle. The effects of the regurgitation is to counterbalance the negative pressure present in the chamber immediately after systole and to put a positive pressure in the ventricle in all periods of diastole. The effect of this positive pressure is to cause an

[1] *Archives of Internal Medicine*, Chicago, 1908, i, No. 1.

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increased tone of the ventricular muscle, as can be shown by comparing the volume curves of the heart in the normal animal and after the production of regurgitation. The probable explanation of this is that the cardiac muscle in aortic regurgitation is "overloaded," for Stewart has determined that, as in an overloaded frog's muscle, the summit of the curve occurs after that of the normal. He shows, moreover, that the collapsing pulse is not due to regurgitation into the left ventricle, but to a reflex dilatation of the peripheral arterioles from stimulation of the ventricular wall by the increased pressure. In some of his experiments, when the operation failed to produce the lesion of the aortic valve, nevertheless, as a result of touching the ventricular wall, the typical features of aortic regurgitation were evident in the records. Stewart explains this reflex as the normal means of preventing the effects of undue pressure in the cavities of the heart. The collapsing pulse in experimental animals is changed to one that is more normal by increasing the peripheral constriction, as, for instance, by compressing the abdominal aorta or by injecting adrenalin; and this is confirmed by finding that compression of the vascular area peripheral to the radial artery in a case of pure aortic regurgitation produces the same result. This fact, the low peripheral resistance in aortic regurgitation, is probably the reason for the frequent presence of capillary and sometimes even venous pulsation.

The Corrigan pulse is more marked when the radial artery is felt with the arm held vertical. This is probably not due to the accentuation of regurgitation, but to the diminished venous pressure and consequent greater capillary flow; for if in this position the veins be constricted, the collapsing pulse tends to disappear. A slowing of the heart beat of itself is probably not harmful if tonus is well maintained, because the volume curves in experimental animals show no greater filling of the ventricle during vagus stimulation than before. The harmful effect of digitalis in certain cases of aortic regurgitation is due not so much to the retardation of the rate of the heart as to the peripheral constriction opposing the vasodilatation which is calculated to relieve the heart.

The blood pressure in aortic regurgitation shows very constant features in experimental animals. The systolic blood pressure remains the same within very narrow limits, the diastolic is invariably lessened, and therefore the pulse pressure, or the difference between them, is increased. This is not borne out by clinical examination in man. The minimum pressure is, as a rule, lower than normal, but the maximum pressure is often much higher. In some cases the increase in the maximum pressure is to be accounted for by the arteriosclerosis, so common in the sclerotic type of aortic insufficiency; but in some cases it may be due to an hypertrophy of the ventricle, which is present in disease, but which was not present in the experimental animal.

To the extra amount of blood which the left ventricle holds at the end of diastole is due (from increased stretching) the hypertrophy which follows aortic regurgitation. If the insufficiency is small, then perhaps the cavity is not dilated sufficiently to give any change in the bulk of the left ventricle; hence occasionally a slight amount of aortic regurgitation may be present without any obvious enlargement of the heart (Krehl). When slight regurgitation is present, even though hypertrophy is marked, compensation may be maintained for many years, as may be seen in aortic regurgitation from rheumatic endocarditis. In a pure valvular lesion, which can, however,

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seldom be supposed in rheumatic cases,[1] the limits of cardiac reserve power, as has been shown by Romberg and Hasenfeld,[2] are little if at all lowered.

Symptoms.—These are best considered under certain groups of cases:

1. **Latent.**—It is surprising how often in the routine examination one meets with aortic insufficiency that has never caused any symptoms. Even in quite young men with no history of rheumatic fever the condition may be detected accidentally, as in the examination for life insurance. Such patients may continue for years doing the ordinary work of life without the slightest inconvenience. A physician consulted me (W. O.) in whom the late Dr. Donaldson, of Baltimore, an expert auscultator, had recognized aortic insufficiency thirty-five years previously. After a very arduous life it had begun to trouble him, and he had slight attacks of angina pectoris.

2. **Acute Aortic Insufficiency.**—In rheumatic fever, in septic conditions, and following a trauma acute insufficiency may arise. The general features of endocarditis are usually present, fever, sweats, etc. There may be nothing to attract attention to the heart itself. Palpitation or tumultuous action may be complained of, and occasional pain. As the condition grows worse there may be attacks of oppression of breathing, and even dyspnœa, but it is surprising, even in severe cases of ulcerative endocarditis, how slight may be the symptoms pointing to the heart. The physical signs are usually well marked—the rapid, forcible action, the throbbing vessels, and, under observation, the signs of insufficiency may increase. In some of the rheumatic cases it may be months before the compensation is established and before the patient is able to get up and move about comfortably and take exercise without shortness of breath. Even in cases that look the most hopeless, with extreme insufficiency and widespread tumultuous action of the heart, the severe features may gradually subside. One friend, of whose life, indeed, we despaired in 1884, in his second attack of rheumatic fever, survived and practised medicine for nearly twenty years. In other cases the acute insufficiency results from rapid destruction of the valve segments in a septic endocarditis, and the picture and course are those presented by this disease.

Some of the cases of the syphilitic aortic insufficiency come in this category. The patients are young men, and within a year or two of the primary infection, usually with the symptoms of angina pectoris, the aortic insufficiency develops in connection with a localized arteritis at the root of the aorta. The symptoms may disappear with antisyphilitic treatment, but the senior writer has not met with an instance in which the murmur of aortic insufficiency has been lost.

3. **Cases with Broken Compensation.**—For years before the breakdown occurs the patient may present a suspicious pallor of the face, the so-called aortic facies. Pronounced vertigo, or on exertion a ringing in the ears, may recur at intervals for months. Shortness of breath on exertion, attacks of nocturnal dyspnœa, uneasy fluttering sensation about the heart, or attacks of palpitation may initiate the breakdown. The pulse becomes somewhat rapid, is feebler, and sometimes irregular; the respirations increase; there are signs of congestion at the bases of the lungs, the liver may be enlarged, and the signs of venous stasis gradually develop; there may be slight œdema of the feet, but general anasarca is rare. The breakdown may be associated with

[1] See Aschoff and Tawara, *Grundlagen der Herzschwache*, Jena, 1906.
[2] *Arch. f. Exp. Path.*, Leipsic, xxxix, 333.

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attacks of cardiac pain, anginal in character. Some of the old hospital patients are admitted ten, fifteen, or even twenty times, always with the same symptoms, shortness of breath, cough, signs of engorgement at the bases of the lungs, albuminuria, and perhaps slight œdema of the feet. In some cases there is marked anæmia. Dyspeptic symptoms are common, and the attack may begin with nausea and vomiting, which may remain troublesome features throughout. Mental symptoms are perhaps more commonly met with in aortic insufficiency than in any other form of heart disease. Delusions may occur even without any loss of compensation. More frequently with the breakdown, the patient begins to lose his mental control, and all sorts of delusions arise, particularly relating to time and place. In the endocarditic form, seen most frequently in young people and often in combination with a mitral lesion, the clinical picture may be that of a slight gradual asystole with venous stasis and dropsy.

Fever, when present, usually indicates either a recurring endocarditis of the sclerotic valves or the presence of a complication.

Physical Signs.—Inspection.—Aortic insufficiency is the only valvular lesion which we can recognize at sight. There is no other condition with which so distinctive a type of throbbing of the arteries is associated. The beating of the carotids above the collar, the visible throbbing in the peripheral arteries, such as the radials and the temporals, and, on ophthalmoscopic examination, the retinal arteries. The peculiar jerk of the foot when the knee is crossed may suggest the diagnosis. Even the head may jerk with each systole. There are one or two conditions which simulate it, which will be referred to later.

Heart.—In children and in young persons the precordia may bulge. In the arteriosclerotic variety there is rarely any deformity of the chest. As the left ventricle reaches a very large size the apex beat is dislocated downward and outward and is usually in the sixth interspace, sometimes in the seventh, and an inch or even two inches outside the nipple line. With full compensation it is regular, forcible, often punctuate, but when the dilatation is extreme and the muscle begins to fail, the impulse is diffuse, often wavy. Although the heart is so large, and, as seen by the fluoroscope, so low, it is very rare that pulsation occurs beneath the costal border in the nipple line. Localized pulsation may be present at the ensiform cartilage and there may be a diffuse impulse extending up the left of the sternum. In children the action of the heart may be very tumultuous. In ordinary cases no pulsation is visible at the base, but with extreme anæmia or when the insufficiency has been rapidly produced, as in ulcerative endocarditis, there may be remarkable pulsations over the aorta and extending into the neck and along the course of the subclavian arteries. These are the cases in which, as Corrigan observed, the diagnosis of aneurism is usually made. And it is often difficult not to make such a diagnosis when one sees a definite impulse in the second or third right interspace, a violent throbbing in the supersternal notch, and the whole front of the chest shaken with each systole.

Arteries.—As already mentioned, by inspection of the arteries alone the diagnosis may often be made. The subclavians and carotids throb violently, and there may be a visible pulsating tumor above the sternal notch. The brachials are visible, sinuous in their course, and with each systole they expand rapidly and as quickly collapse. Similar large pulsations may be seen in the radials and the temporals and even in some of the smaller vessels.

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In no other state do we see such widespread and peculiar throbbing in the peripheral arteries. Occasionally this diffuse vascular impulse is evident in the solid organs, as the liver and spleen, in which a pulsation may be felt, and the whole pharyngeal region may throb visibly and change in color with each systole. The beating in the retinal arteries may be very forcible and even be distressing to the patient.

Capillaries.—The capillary pulse, first pointed out by Quincke, is seen in a great majority of cases. It may be looked for on the nails, or a line may be drawn on the skin, or it is well seen by the pressure on a bit of glass upon the lip. The finger nail is a very satisfactory locality to see it, but it requires good eyes and always good light. Occasionally it is present in a very remarkable form. The palms of the hand blush with each systole and become pale in diastole. Held up against the light the change in color of the skin may be visible six or eight feet away.

Veins.—Pulsation in the cervical veins is common, but it may be difficult to distinguish from the communicated throbbing of the violently beating carotids. The superficial veins are often very full, and it is one of three or four conditions in which pulsation is common particularly in the back of the hand and in the veins of the arm.

Palpation.—Depending upon the stage of the disease, the cardiac impulse is felt to be forcible, punctuate, heaving at the apex, or, when compensation fails, widespread, wavy, and diffuse. The whole front of the chest may be lifted during systole of the huge heart. The shock of the sounds at the apex is occasionally felt. A systolic thrill is rare at the apex. A thrill is sometimes present with the qualities of the mitral presystolic thrill, and it may even terminate abruptly in a first sound. In the endocarditic type of the disease, with the associated stenosis, a thrill is not uncommon at the base, more commonly systolic, but sometimes double. A very marked diastolic thrill may be caused by a calcified spur in the valve.

The arteries feel large and are very commonly sclerotic. From the character of the pulse alone the diagnosis may be often made. Even the handshake may suggest the lesion, or as in the story told of Opoltzer, the characteristic quality may be perceived by touching the foot of a patient as he rests in bed. The pulse beat (pulsus celer) is sudden, forcible, and then drops immediately, resembling the beat of a water-hammer (water-hammer pulse). The abrupt shock-like sensation communicated to the finger is followed by a sudden collapse—hence the name collapsing pulse. By elevating and grasping the arm about the middle, the palm of the hands toward the radial and ulnar arteries, the jerking quality is best perceived. It may be felt in the finger tips and even in the toes. The hand laid upon the dorsum of the foot may feel it with great distinctness. With anæmia it becomes very marked. The pulse is regular, except during certain complications and toward the close when the heart muscle fails. The sphygmographic tracing is very characteristic—a straight and high line of ascension showing the abrupt and forcible distention of the artery, a rapid line of descent forming a very acute angle with the upstroke. The carotid and radial pulse is stated by some to be retarded, particularly by P. Chapman,[1] who has made an interesting study of this point.

A thrill may sometimes be felt over the larger vessels. At the root of the

[1] *Lancet*, 1898, ii.

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neck the arteries may feel very voluminous, and even in diastole may be so distended, particularly in young persons, that the diagnosis of aneurism is made.

Auscultation.—A diastolic murmur is heard at the base of the heart, of maximum intensity over the sternum opposite the second or third interspace, sometimes at the left border of the sternum at the third or fourth costal cartilage. Authors differ very much in assigning the point of maximum intensity to this murmur. The French, particularly, place it at the right border of the sternum. The truth is it varies greatly in different cases. In

FIG. 18

Aortic regurgitation. The pulse tracing shows a rapid rise and fall.

the endocarditic form and when stenosis is present the murmur may be most intense at what is known as the aortic cartilage. In the arteriosclerotic form, particularly when the murmur is soft, the maximum is more commonly at the left border of the sternum in the third or even the fourth interspace. The variation has been thought to depend upon the position of the insufficient segment. No murmur may be present to the right of the sternum in the situation at which one usually listens. The murmur may be so soft as to be readily overlooked, or it may only be rendered audible by exertion. A diastolic murmur may disappear under observation, or it may change

FIG. 19

Aortic regurgitation. The pulse tracing shows the effect of arteriosclerosis on the collapsing pulse, the fall being rendered much less sudden because of the increase in the peripheral pressure.

its character. In a few cases, though insufficiency is present, a diastolic murmur is not heard. In personal experience this has been very rare, but it may occur in the arteriosclerotic form. On several occasions the senior author heard a soft diastolic murmur, when postmortem the valves by the water test appeared to be competent; but in these cases the segments were a little sclerotic, and there may have been dilatation of the aortic ring.

The quality of the diastolic murmur varies greatly in different cases. It may be a soft long-drawn murmur, only just audible, or an intense blowing murmur, while in other cases it has a musical quality. In a majority of the

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cases there is a double murmur; in the endocarditic form the systolic is usually rough and rasping in quality, in the arteriosclerotic it is soft. A systolic bruit is not always present. The normal aortic second sound may be audible, but in a majority of cases it disappears altogether. The murmur is propagated down the sternum, and may even be intense at the ensiform cartilage. As a rule, it is not audible beyond the left parasternal line at the level of the fifth rib. In the common cases of the arteriosclerotic form it is not heard up the sternum or in the vessels of the neck. When there is dilatation of the aorta and much roughening of the intima, the diastolic murmur may be well heard at the base of the sternum and in both carotids. So also the loud rough systolic murmur in connection with aortic stenosis may be transmitted upward.

Change in posture does not, as a rule, make very great difference, except intensifying the murmur. Occasionally the alteration from recumbent to erect position may bring out a musical quality.

A systolic murmur of mitral insufficiency is present with the combined aortic and mitral lesions in the endocarditic group, particularly in children; in the arteriosclerotic group when the mitral segments are themselves curled and shortened and with great dilatation of the ventricle when relative insufficiency of the valve occurs. In many cases no apex systolic murmur is present.

The Apex Diastolic Murmur (*the Flint Murmur*).—In a majority of cases of aortic insufficiency, as the stethoscope is passed along the fifth rib just beyond the parasternal line, a change is noticed in the character of the murmur during diastole. The soft blowing character is lost, and as the nipple line is approached a murmur is heard with a rumbling, purring quality, at once suggestive of the well-known one heard in mitral stenosis. Austin Flint, who first described this murmur, was astonished to find at the postmortem on two cases in which it was present that mitral stenosis did not exist. It has been studied with great care by numerous observers, and for many years at the Johns Hopkins Hospital our attention was specially directed to it in connection with the very rich material at our disposal. The results have been published in a paper by Thayer.[1] The murmur is common, being heard in slight grades in a majority of cases. It is apical in situation, usually above and to the inner side of the maximum apex beat. It is often very localized. It may occur throughout the entire diastole or through the terminal portion, being purely presystolic, or in some instances it is distinctly mid-diastolic. The striking feature is its rumbling and vibratory quality, such as is so distinctive in the presystolic murmur of mitral stenosis. Sometimes there is a crescendo character, and it may terminate abruptly in a sharp snapping first sound. When to these features are added a thrill and a shock of the first sound felt on palpation, it is not surprising that the diagnosis of mitral stenosis is made. Time and again under these circumstances we have discussed the possibility of the existence of mitral stenosis, every cardiac physical sign of which was present. This difficulty is apt to occur in young persons with the endocarditic form, in whom the possibility is always present of the involvement of both orifices. In the arteriosclerotic form and in the subjects of syphilis the chances are always against

[1] *American Journal of the Medical Sciences*, 1901, cxxii, p. 538

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mitral stenosis, even with a combination of physical signs which almost compel the diagnosis.

Auscultation of the Arteries.—Along the subclavians and carotids the diastolic murmur may sometimes be heard. Occasionally the double murmur is transmitted. As a rule, in the arteriosclerotic form the diastolic murmur is not heard above the level of the second costal cartilage, and is not transmitted into the arteries. The most characteristic phenomenon over the larger arteries, particularly the femoral, is the "pistol-shot" sound, a short, sharp systolic shock, and, as Traube pointed out, a second sound feebler than the first, co-incident with the diastole of the artery. The latter is not always heard. With very slight compression of the artery, particularly at the femoral, a double murmur is heard—Durosiez's sign.

Diagnosis.—No heart affection is so easy to recognize, and there is not one less frequently overlooked. The diastolic murmur, and the visible collapsing pulse are pathognomonic. The mistake most likely to arise is the one mentioned by Corrigan in his original paper, namely, the diffuse throbbing of the aorta and the large vessels suggest aneurism. The diagnosis will be considered under that section. A diastolic murmur at the base is heard in several other conditions. Insufficiency of the pulmonary valves occurs in a few instances in connection with long-standing mitral disease. The conus arteriosus and the ring of the pulmonary artery are dilated, and there is relative insufficiency of the valve. The murmur is sometimes called after Graham Steell, who has called special attention to this lesion. It is more often diagnosed than existent. In several cases in which we thought it to be present in young persons the lesion proved to be aortic. The situation in the left intercostal space close to the sternum is of no moment whatever, as this is a common situation for the aortic systolic murmur. The two important points really are the existence of old mitral disease and the absence of the characteristic vascular phenomena of aortic insufficiency. A diastolic murmur heard over the sternum may be of venous origin, and is met with particularly in Graves' disease. Cases have been described, too, in young persons in whom no definite cause could be assigned. Some of these cases may have been due to pressure of glands on the veins. Occasionally the cardiopulmonary murmurs are diastolic, and to this class in all probability belong the so-called transitory diastolic murmurs which are reported at intervals in the literature.

Rupture of the valve is indicated by a sudden onset after exertion, with pain, tumultuous action of the heart, and a loud, perhaps musical, diastolic bruit. The arteriosclerotic form is rare under thirty-five years of age. It is associated with signs of arterial disease, and the etiological factors are drink, hard work, and the stress and strain of life, or syphilis. Endocarditic cases occur in the young with a history of rheumatism or of some severe infection. More frequently than in any other form the orifice is narrowed, and there is a loud, rasping, systolic bruit. Relative insufficiency occurs in connection with dilatation of the aorta or with aneurism. The murmur is usually soft, and it may be heard high on the sternum, and with extreme atheroma a systolic murmur is usually present. In very old persons the insufficiency and stenosis are usually combined, and there is a rasping systolic murmur with a thrill.

Special Features and Accidents of the Disease.—Aortic insufficiency is a disease of accidents and surprises. Sudden manifestations may

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occur after a long period of latency. Among these the following are the most important: (1) The sclerotic aortic valves may be attacked by endocarditis, which may assume the ulcerative form. (2) In the sclerotic variety, in which the root of the arch and the coronary arteries are very apt to be involved, angina pectoris is a common event, and death may occur in the first attack. In the syphilitic form recurring attacks may precede the insufficiency, the process of which may be gradually traced. (3) Sudden death is more common in aortic insufficiency than in any other valvular disease. It may occur while the patient is at rest, even while asleep; more frequently it follows a sudden exertion or a violent emotion. While it may be due to acute dilatation, it is more probable that in a considerable proportion of the cases the coronary arteries are involved and there is a sudden interference with the circulation of blood in the heart muscle itself. (4) Embolism is not so common as in mitral disease. A vegetation growing on the sclerotic valves may be dislodged and plug a cerebral vessel, or a calcified fragment or an atheromatous flake may become detached and pass to the brain or to one of the peripheral arteries. In one instance the formation of a popliteal aneurism followed the dislocation of a fragment from the valve, which had been associated for years with a musical diastolic murmur. Following the accident the quality of the murmur changed entirely.

Prognosis.—Recovery is stated to occur, even by observers so careful as Potain, Leyden, and Gerhardt. Personally, the senior writer has never seen a case in which the diastolic murmur has disappeared, although in several syphilitic patients it has become very much less definite. It does not seem likely, as has been suggested, that when only one valve is affected the other two could enlarge and so compensate for the defect. The prognosis varies with the different varieties. The endocarditic is the most hopeful, except in young children with a combined mitral lesion; but in young men compensation may be perfect, and for years there may be no symptoms. After an active life the patient may reach a good old age. Recurrent endocarditis, the chronic septic form or the rheumatic variety, may attack the valves, but such a patient may go through serious illness, even severe rheumatic infections, and recover with a useful heart. In the syphilitic form the prognosis is bad, unless an early diagnosis is made and prompt treatment given. In the arteriosclerotic form, which comes on after the fortieth year, the prognosis is bad, as the root of the aorta and the orifices and the trunks of the coronary vessels are apt to be involved, so that the nutrition of the heart is soon interfered with. These are patients in whom sudden death is apt to occur.

Both in the young and in the aged, moderate stenosis lends a rather more favorable prognosis to the condition. Combined with mitral insufficiency, due to disease of the valve, the outlook is not so good. In adults slight relative insufficiency of the mitral is a favorable feature.

STENOSIS OF THE AORTIC ORIFICE.

This is the rarest of all forms of valvular disease, and usually with it is associated some grade of insufficiency.

Incidence.—In the Edinburgh Infirmary Statistics it occurred alone in 40 cases out of 1914, and in 152 cases with another lesion. Among 670 cases

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of valvular disease Romberg found only 28, among which there were only 17 without simultaneous disease of other valves.

Etiology and Morbid Anatomy.—As a rule, the process is chronic, but in a few cases one meets with an acute stenosis due to the growth of very luxuriant vegetations on the valves. There are two great types of the disease, the endocarditic and the arteriosclerotic.

Following endocarditis from any cause, but more particularly from rheumatic fever, the vegetations organize, the edges of the valve thicken, become adherent, sclerotic, and finally calcareous. The segments may be infiltrated with lime salts, and even the aortic ring itself, the whole forming a rigid, calcified mass perforated at one spot by a rounded, oval, or linear orifice. Very varying degrees of involvement of the segments are met with. As a rule, they are greatly deformed, but sometimes only the margins are diseased and the narrowing results from the calcified nodular outgrowths. Indeed, Rendu, quoted by Barié, reports a case in which the narrowing was due to an enormous hypertrophy of the nodules of Arantius. The degree of stenosis is very variable, and may reach a remarkable grade, so that the orifice is not more than a few millimeters in diameter. Insufficiency is always present, the degree depending on the size of the orifice. Of course, when there is calcification and rigidity, there is no possibility of closure of the orifice during diastole. In this endocarditic form the aorta itself is not involved. The mitral valve is almost always affected, but in a certain number of the cases the aortic alone is attacked.

In the arteriosclerotic type the lesion of the valve is part of a widespread arterial degeneration. In men at the middle period of life the sclerosis is not often associated with stenosis. Occasionally there is a slight grade, but one may examine anatomically 25 or 30 cases in succession of sclerosis of the aortic valves without any narrowing of the orifice. In a few cases the edges of the valves coalesce and some narrowing results from atheromatous changes with calcification. The most characteristic form of arteriosclerotic stenosis is seen in elderly persons. It comes on insidiously, and may attain a very pronounced grade without causing any symptoms. In a special variety, described by Norman Chevers, the stenosis does not involve the ring, but the infundibulum or the part below it. This usually follows an extension of a chronic mitral fibrosis.

The heart is enlarged, sometimes very greatly, but rarely reaching the size of that of pure insufficiency. Early in the disease there may be pronounced hypertrophy without much dilatation, and clinically the enlargement may not be very great. Theoretically, with an obstruction at the aortic orifice the ventricle is unable to expel the usual amount of blood into the aorta. The cavity at the beginning of diastole still contains blood, so that at the beginning of systole it is fuller than normal. This causes a greater stimulation of the muscle fibers of the walls, more pressure per unit area is exerted on the contained blood, and more is forced into the aorta through the obstruction. The stimulus of a resistance to contraction during its activity, *i. e.*, when the muscle is overloaded, causes systole to be prolonged from 7 to 30 per cent. of the normal. This differs from the conditions in aortic regurgitation, in which the systole is little if at all prolonged. In this, however, there is no extra resistance to contraction during the period of activity. If the extra force expended by the ventricle is sufficient to discharge the normal amount of blood into the aorta, the cavity is not increased in size, and with

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the development of hypertrophy the circulation goes on as before. But if the stenosis is greater than can be overcome by the ventricle, or if the muscle of the ventricle is enfeebled, there is residual blood at the end of systole and the ventricular cavity is permanently enlarged. A third stage is that in which not only the ventricle but also the left auricle is overfilled at the beginning of systole. The auricle, by increasing the vigor of its contractions, may for a time be able to cope with it, but further failure may set in, leading to the same series of changes as occurs in mitral disease—congestion of the lungs, hypertrophy followed by failure of the right ventricle, venous engorgement, and œdema.

The estimation of the blood pressure in aortic stenosis shows that little if any difference exists from the normal. The number of recorded cases is, however, not great. We should expect to find that the maximum and minimum blood pressures estimated by reliable instruments were nearer one another than in a normal person.

Symptoms.—No heart lesion is more frequently latent. In the arteriosclerotic form years may elapse before the patient experiences any discomfort. Indeed, it is one of the diseases, to use an expression of Oliver Wendell Holmes, that may promote longevity. It has helped many a man to become an octogenarian. In young persons, following endocarditis, symptoms on the part of the heart are more frequent—palpation, irregularity, distress on exertion, and the cardiac reserve is readily exhausted. It is not always easy to separate the effects of the aortic from the mitral disease if present. In old persons vertigo is a common symptom, and shortness of breath on exertion. An extraordinary degree of muscular vigor and good health may be maintained, but the capacity for exertion is greatly reduced and breathlessness follows any extra effort. Attacks of angina occur in some cases, in one of which death may take place. Many patients have a sense of oppression and distress beneath the sternum on the slightest exertion or emotion. Cardiac failure may occur with venous stasis and all the signs of cardiac dropsy. Sudden death is not very uncommon. In others, intercurrent affections, such as cystitis and a consecutive nephritis, may cause death.

Physical Signs.—Inspection.—In young persons the precordia may bulge and signs of hypertrophy are present. In these cases the degree of enlargement of the heart depends much more upon involvement of the mitral and the amount of insufficiency of the aortic cusps. When these are present, there may be a great deal of dilatation and a very large heart. On the other hand, with pure stenosis there may be little or no hypertrophy, and the apex beat may be dislocated a little down and out, but the organ is not greatly enlarged. On palpation the apex beat is easily felt in the fifth or sixth interspace, forcible and regular. Many years ago Traube pointed out that in a considerable number of cases the apex beat was absent.

Percussion.—Percussion shows slight increase of the cardiac dulness downward and to the left, varying with the degree of dilatation. On *palpation* a systolic thrill is felt at the base, of maximum intensity in the second right intercostal, propagated up the sternum and sometimes felt in the carotids and subclavians. On *auscultation* a loud, rough systolic murmur is heard of maximum intensity at the base. It is harsh, rough, rasping, usually protracted, in other instances high-pitched, whistling, and musical. It is propagated along the vessels of the neck and along the subclavians. It is some-

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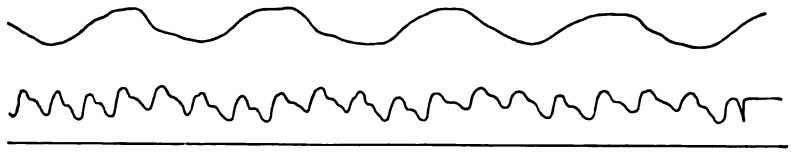
times heard with great intensity toward the apex of the heart, even when there is no mitral disease. The first sound is usually absent or very feeble. The second aortic sound is, as a rule, absent or replaced by a diastolic murmur of varying intensity and quality. Sometimes the second sound is quite well heard, but it depends on the measure of retention of the elasticity of the aortic segments. It is not probable that with uniform calcification and rigidity any sound could be produced. A peculiarity more commonly met with in aortic stenosis than any other valvular lesion is the murmur audible at a distance from the chest wall. This was noted by Stokes in the case of a politician in whom the murmur was so loud that it could be heard by his colleagues sitting about the table. Very many such cases are reported in the literature.[1] The pulse in aortic stenosis is slow, small, hard, and regular. The rate does not often fall below 60, and occasionally it is permanently at 40. In the senile cases the Stokes-Adams syndrome may be present, and syncopal attacks or epileptiform seizures occur. The pulse is small because the orifice permits of a comparatively small amount of blood, and the smallness of the beat may contrast in a striking manner with the force

FIG. 20



Aortic stenosis. The upper curve is the respiration, the lower the pulse curve. The latter shows the small amplitude and the rounded top of the primary wave.

of the cardiac pulsation. Hardness is, as a rule, associated with the sclerosis of the vessel. Sphygmographic tracings are very characteristic, and show a small pulse wave with a rounded or flattened summit with a very oblique line of ascent and almost without dicrotism.

Diagnosis.—The disease is frequently diagnosed when it does not exist. To inexperienced observers any loud murmur at the base suggests stenosis, whereas that lesion is the last to be considered. Slight roughening of the valves, roughening of the intima of the aorta, and hæmic conditions are common causes of the systolic murmurs at the aortic area. With aneurism, too, a loud murmur is occasionally present. Stenosis of the pulmonary orifice has very much the same features on palpation and auscultation, but it occurs, as a rule, in young persons, is not propagated to any extent into the vessels of the neck, and is loudest to the left of the sternum. As a rule, there is very little difficulty, if one takes into consideration the thrill and the character of the murmur in combination with the state of the heart and the pulse.

Prognosis.—In young persons it is bad, particularly with associated mitral disease. Sometimes in the pure aortic stenosis following rheumatic fever the compensation may be maintained for many years, but, as a rule, the outlook is not so good as in the late sclerotic form of insufficiency. In

[1] See Ebstein, *Deutsch. Archiv f. klin. Med.*, Band xxxviii.

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any case, it is a lesion that takes many years for its formation, and many patients succumb to accidents, not to the disease itself. The most favorable cases are those in which, as a result of a slow, presenile sclerosis the orifice has been gradually narrowed. If the patient accepts the conditions, lives a peaceful, easy life, the heart lesion itself may promote longevity. For many years the senior writer followed with interest the lives of two old men with typical features of aortic stenosis. One was an Anglo-Indian who lived to be over ninety years of age. He had a very large heart and a thrill at the base which could be felt through his overcoat and was audible some distance from the chest wall. The other died at the age of ninety-two years of bladder complications. The patient was about sixty years of age when the aortic stenosis was diagnosed by Walshe.

Loss of compensation is usually the result of myocardial changes, and once gone is rarely restored.

INSUFFICIENCY OF THE MITRAL VALVES.

When from any cause the mitral segments do not close during systole of the ventricle a variable amount of blood passes back into the left auricle through the insufficient valves. This is one of the most common of all cardiac lesions. In the Edinburgh figures, already quoted, among 1914 cases there were 585 with mitral insufficiency alone, and 463 in which it was combined with another lesion, in 231 of these this being mitral stenosis.

Forms.—There are three great groups of cases, the endocarditic, the chronic sclerotic, and the relative or muscular. In a few cases the insufficiency may follow rupture of one of the segments.

Endocarditic Form.—This, the most common, is met with in young persons as a complication of the acute infections, more particularly of rheumatic fever. The general effect of endocarditis upon the valves has already been described. The special danger of the rheumatic form is owing to the fact that the segments are the seat of a productive valvulitis. In certain cases insufficiency is rapidly produced by destructive lesions which erode the chordæ tendineæ and destroy the segments, so that within a week or ten days a high grade of insufficiency is produced. In a large proportion of all cases there is no actual erosion of the valve itself, but the insufficiency is caused by a gradual shrinkage of the newly formed connective tissue in the substance of the valve. When this goes on very rapidly, as is sometimes the case, both curtains are rolled up as it were, leaving a widely open orifice. This is not nearly so common as the slower process in which the constricting cicatrization draws together the margins of the valves, so that with the insufficiency there is some grade of narrowing. The orifice may admit the thumb, or not more than the tip of the little finger. The edges are smooth, greatly thickened, often of a cartilaginous hardness, and the chordæ tendineæ are greatly thickened, shortened, and often fused together. It is quite frequent to have beads of fresh endocarditis on the margins of the thickened valves. Lime salts may be deposited and the valves and ring together form a solid calcified mass.

Arteriosclerotic Form.—In the arteriosclerotic form without any preliminary acute endocarditis the valves gradually thicken, the edges become curled, slightly shortened, the chordæ tendineæ become thickened, the orifice is

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slightly narrowed, lime salts are deposited in the valves, and, as age advances, the whole valve and ring become a rigid and calcified membrane. In a slight degree sclerosis of the mitral valve is met with in all persons over sixty years of age, and is an expression of the wear and tear of work.

Relative Insufficiency.—Relative insufficiency, by far the most common form, occurs whenever dilatation of the mitral ring reaches such a grade that the normal valve segments are no longer able to close it. Known by the names of functional, muscular, or, more commonly, relative insufficiency, the most common cause is loss of tone of the muscle which surrounds the mitral ring. This occurs in many blood conditions, such as chlorosis and pernicious anæmia, in fevers, in many neurotic states, as neurasthenia, in Graves' disease, and in all cases when the dilatation of the ventricle from any cause reaches a certain grade.

Insufficiency due to rupture of the chordæ tendineæ, or of one segment, is very rare in the healthy valve, but a number of cases have been described; most frequently the chordæ tendineæ of the anterior segment are ruptured.

Symptoms and Physical Signs.—Many patients with mitral insufficiency never present any symptoms. In a still larger proportion symptoms are only present at the terminal stage of a long and silent history. The cases which give rise to symptoms earliest are those of insufficiency following the endocarditis in children, particularly in the tragic group which makes rheumatic fever so malignant an infection. Relative insufficiency in the fevers, in chlorosis, in anæmia, may never give rise to symptoms. No valvular lesion presents such diversity of features in regard to the duration and severity. There are cases in children in which the valve segments are rapidly curled and rendered so insufficient that the limits of compensation are quickly reached. On the other hand, there is no valve lesion in which we see more perfect and more enduring compensation. The marvellous manner in which the heart is able to carry on the work illustrates the remarkable response of muscle to calls made upon it very gradually. It reminds one of Montaigne's illustration of the force of custom: "He seems to me to have had a right and true apprehension of the power of custom who first invented the story of a country woman who, having accustomed herself to play with and carry from the hour of its birth a calf in her arms, and daily continuing to do so as it grew up, obtained by this custom that when grown to be a great ox she was still able to bear it."

Pathological Physiology.—Depending upon the degree of insufficiency of the valve, a variable amount of blood is forced back into the left auricle during its diastole and while it is filling from the pulmonary veins. With this extra amount of regurgitated blood the auricle reaches its normal distention sooner than previously. The pressure at the end of diastole is greater than at this period were there no valvular deficiency, the muscular fibers of the auricle are more stretched than normally, and, as we know from v. Frey's[1] experiments, the muscle is stimulated to a greater contraction. If the more powerful contractions, either immediately succeeding the lesion of the valves or ultimately by reason of hypertrophy, can force into the ventricle the normal amount plus the extra blood which was regurgitated, the circulation becomes compensated and the effects of the insufficiency do not extend farther than the left auricle. Over and above the

[1] *Deutsch. Arch. f. klin. Med.*, 1889, p. 358

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evidence of regurgitation by auscultation, very careful percussion may give a higher pitched note at the apex of the left lung in front, and with the *x*-rays a marked increase in the amplitude of pulsation in the position of the left auricle may be seen.[1] A method has recently been devised by Minkowski[2] for obtaining a graphic record of the pulsation of the left auricle, and this might be of use in determining the presence of increased activity of this chamber. The left ventricle must accommodate the additional blood from the auricle, and in consequence its cavity becomes larger, its pulsations (owing to the slight stretching) more forcible, and hypertrophy of the muscular walls follows.

In the condition just described it has been assumed that the normal closure of the pulmonary veins took place during the systole of the auricle. We do not know at present how this is accomplished, but from the analogy of the right auricle, in which muscular bands are disposed to that end, we may conclude that it is affected by the same process.[3] With further dilatation of the cavity the orifices will remain open during the systole and the heightened pressure will be communicated to the blood in the pulmonary vessels. The dilatation of the auricle does not go beyond a certain point, partly because of the opening of the orifices of the pulmonary veins and partly from an increase in the connective tissue, which has been shown to accompany compensatory hypertrophy.

MacCallum and McClure,[4] in studying the effects of artificial lesions of the mitral valve in animals, have found that the pressure in the systemic arteries falls markedly, that in the left auricle rises, and that in the pulmonary artery may rise or fall; a high degree of insufficiency produces a fall of pressure in both the systemic and pulmonary systems; in slight insufficiency it usually rises. Whatever the pressure, the lungs invariably contain a larger amount of blood, for it has been shown that the venous pressure falls with a fall in the arterial pressure. The depletion of the systemic arteries is made up either by a constriction of the peripheral vessels, or by an increase in the volume of the blood. In the case of a small deficiency of the mitral valve the ventricle enlarges to receive the normal amount of blood from the auricle plus a portion of that regurgitated, and rejects into the aorta something less than the normal amount. If the ventricle has sufficient power to eject all the blood poured into it, the circulation becomes compensated; if, on the other hand, the power of the ventricle fails, it dilates.

In what way the hypertrophy of the right ventricle helps is an open question. MacCallum and McClure have shown that, so far as the pressure is concerned, the lung capillaries may be looked upon almost as a rigid tube, for the pulsations of the left ventricle are transmitted directly to the pulmonary artery and with such little loss of time that the pressure wave of the left ventricle is opposed to the action of the right ventricle during the systole.

A mitral insufficiency compensated for ordinary conditions by the right ventricle may continue for a long period of years. If this chamber fails

[1] Abstract in *München med. Woch.*, 1907, p. 849. See also Bonniger, *Deutsch. med. Woch.*, 1907, p. 333.

[2] *Deutsch. med. Woch.*, 1906, xxxii, p. 1248.

Keith describes a very probable method of closure of the orifices of the great veins into the right auricle, *Lancet*, 1904, i, p. 555.

[4] *Johns Hopkins Hospital Bulletin*, 1906, xvii, 260.

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either from increasing deficiency of the mitral valve or from changes in its muscle, the tricuspid valve becomes incompetent. The right auricle becomes dilated and hypertrophied. The orifices of the veins are no longer closed during systole, and finally the pressure from the right ventricle is communicated to the venous system which becomes engorged. With great insufficiency of the mitral valve considerable pressure is communicated during systole to the auricle, whose walls probably become so stretched that the muscular fibers are injured and the contractions become very feeble. The increased pressure in the auricle and pulmonary bloodvessels gives rise to the thickened endocardium, so frequently seen in the former, and atheroma in the latter. In the first stage the left ventricle hypertrophies as a result of the increased pressure and compensatory dilatation at the end of diastole, caused by a more vigorous left auricle. Even with failure of the left auricle the pressure in it communicated from the right ventricle is sufficient to maintain the filling of the left ventricle, the hypertrophy of which may keep pace with the further dilatation, and it may become very large and thick. Under these conditions the normal filling of the arteries would be maintained, but with failure of the hypertrophy and loss of the contractile power of the muscle, the arteries become improperly filled and the blood pressure tends to fall. With the lessened blood pressure comes an increase in the rate of the pulse. The cause of the irregularity of the pulse in mitral disease is unknown; possibly it is due to the same condition as that suggested by Mackenzie in mitral stenosis.

Little that is definite can be said of the blood pressure in mitral regurgitation. The condition of the pulse is no evidence of the height of the pressure estimated by clinical instruments, for cases are recorded with a blood pressure of 140 mm. Hg., in which the pulse was scarcely to be felt. Hensen[1] does not agree with v. Basch, who says that the blood pressure in mitral disease is low, for oftentimes, according to his observations, it is distinctly above the average. With any irregularity of the pulse the maximm blood pressure varies much, sometimes being only a little over 100 mm., at other times reaching 140 mm. or more. The feebleness of the pulse in mitral disease, when the pressure is high, may be due to peripheral constriction of small arteries to compensate for the underfilling of the arterial system, but of these peripheral mechanisms we have little knowledge.

Symptoms.—The symptoms may be divided into two groups. While compensation is still good there are many minor manifestations, as the pain and breathlessness on exertion. When the insufficiency is extreme, the patients have a bluish tint of the cheeks and ears, giving the very suggestive appearance, the "mitral facies." The hands and feet may be blue, and in very long-standing cases the fingers may be clubbed.

Occasionally in children the degree of cyanosis reaches that met with in congenital heart disease, but it is never so extreme as in the cases of adhesive pericarditis with great hypertrophy of the heart and proliferative perihepatitis and peritonitis. Breathlessness on extra exertion may persist for years. These patients are especially liable to bronchitis in the winter. One of the most remarkable features is the recurrence, over long periods of years, of hæmoptysis. In Philadelphia the senior writer saw frequently a physician who had had his first attack of hæmoptysis during the Civil War.

[1] *Deutsch. Arch. f. klin. Med.*, 1900, lxvii, p. 512.

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Tuberculosis was then suspected, but a mitral lesion was discovered. On and off during twenty-five years he had had attacks of quite sharp hæmoptysis, sometimes with great relief. He had a greatly enlarged heart and a rasping apex systolic murmur audible all over his chest.

Broken compensation or decompensation may set in abruptly following any extra exertion, a severe mental shock or a protracted illness. Palpitation, which objectively may have existed for years, becomes evident and distressing to the patient. The shortness of breath increases. The patient wakens at night, perhaps abruptly in a paroxysm of shortness of breath, or there may be distressing "sleep starts," in which, just as he is dropping asleep, he wakens gasping as though his heart had stopped. The most distressing single feature is the oppression in the chest associated with the breathing. The slightest exertion brings it on, and the patient may at last be unable to move from his bed, or the dyspnœa may continue even when he is at rest. Very soon the signs of venous stasis are present. There is œdema of the feet, which gradually extends upward; the abdomen begins to swell, the liver is enlarged, and there is a slight jaundiced tint to the skin. The anasarca becomes extreme and the serous sacs may become dropsical. The urine is scanty and albuminous, and contains tube casts and sometimes blood corpuscles. The patient is restless, often sleepless at night, and there is anorexia and sometimes vomiting. With judicious treatment, even with rest alone, the attack may pass off and months, or even years, may elapse before a breakdown occurs. Only too frequently it happens that once compensation has been broken, the patient is very liable to subsequent attacks.

Among special features which may be mentioned are embolism, either from a clot in the left auricle or from a vegetation on the edge of the thickened valves. A remarkable thrombosis may occur in the distended veins, particularly in the jugular or in the brachials. There was one extraordinary case at the Johns Hopkins Hospital—a woman who was under our care for many years. She had half a dozen attacks of thrombosis in different parts of the body.

A remarkable feature of these very chronic cases of mitral insufficiency is the recurrent hydrothorax, which may be the only feature of the disease. It is most common on the right side, possibly due to compression of the azygos veins. It may be the only feature, and there are instances in which the patient has been up and about, and able to attend to his work, but has had to have the right pleura tapped every week or even at shorter intervals. Perhaps the most extraordinary case on record of this kind is reported by W. T. Gibb, of New York; a physician with combined aortic and mitral disease was tapped 311 times in 580 days, but was able to be up and about and do almost anything until two days before his death.

The hepatic symptoms of heart disease are met with in the most typical forms in mitral insufficiency. With the establishment of tricuspid insufficiency there is a swelling of the organ, the edge of which may be felt a hand's breadth or more below the costal border. On careful inspection diffuse pulsation may be seen, and the organ may be felt to swell with each systolic impulse. A slight tinge of jaundice is common. In the long-standing cases the liver becomes greatly enlarged, the connective tissue increases and the state of cardiac cirrhosis is gradually produced. The organ is large, smooth, and hard, with rounded edges. In very protracted

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cases shrinkage may occur. In an interesting group of cases for a year or more toward the close, the features are entirely hepatic and the patients come under observation with recurring ascites, which may require tapping every few weeks. This accumulation of fluid in the peritoneum may be the only form of dropsy present. While it is not always possible to exclude the influence of alcohol, yet there are cases in which the cirrhosis seems to be altogether a late effect of the stasis.

Physical Signs.—Inspection.—In children the precordia may bulge and there is usually a very large area of visible pulsation, undulatory along the left sternal border with a more definite apex beat in the fifth or sixth, sometimes the seventh interspace. There may be visible pulsation to the right of the sternum and a marked impulse in the second and third left interspace. Frequently the whole front of the chest throbs visibly, and in mitral insufficiency we see more widespread impulse than in any other cardiac condition. The visible heart beat may extend from one anterior axillary line to the other. The impulse is usually very strong at the ensiform cartilage, and the heart may be so depressed and enlarged that there is a forcible, punctuate impulse of the right ventricle below the left costal border in the parasternal or even the nipple line. In the arteriosclerotic type in elderly persons with very slight hypertrophy of the left ventricle the impulse may be scarcely visible. In very long-standing cases the apex beat may be far out, even in the midaxillary line. In relative insufficiency the impulse may be scarcely visible, and may be only a little if at all to the left of the nipple line.

The veins at the root of the neck are usually full, and there are the pulsations which will be more fully described in connection with tricuspid insufficiency. In the stage of decompensation, at the jugular bulb, just above the right sternoclavicular joint, there may be a large ovoid tumor as big as an egg.

Palpation.—The degree of shock will depend upon the extent and force of the cardiac impulse which may be very strong and heaving. A systolic thrill at the apex region and transmitted into the axilla, is not so common as the presystolic in mitral stenosis, but in the long-standing cases in adults it may be very rough and rasping. The shock of a first sound is rarely to be felt, but the shock of the second may be widely diffused.

Inspection and palpation are the only safe guides in estimating the organic character of mitral insufficiency; if the apex beat is dislocated outward and very forcible, we may be certain that there is an actual lesion present.

Percussion.—The cardiac dulness is increased, particularly in a lateral direction, and may extend far to the right, reaching even to beyond the parasternal or nipple lines. The upper limit may be at the second rib and in extreme cases far to the left, even to the midaxillary line. Not even in the cor bovinum of aortic insufficiency do we find, particularly in children, such an extended area of cardiac flatness.

Auscultation.—A murmur accompanying or obliterating the first sound, of maximum intensity at the apex, and transmitted toward the axilla is the most distinctive single physical sign of insufficiency of the mitral segments. Its quality may vary from a soft blowing to a loud, harsh, rasping murmur; or it may have a distinctly musical quality, which is perhaps more frequently heard with mitral insufficiency than in any other lesions. The point of maximum intensity is, as a rule, at the apex or a little inside it.

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At times it is heard loudly along the right margin of the sternum and, as Naunyn pointed out, it may be even of maximum intensity at the second or third left interspace. The special direction of propagation is along the left pectoral fold into the axilla, and the murmur is often loud and distinct at the angle of the scapula. In long-standing cases with great hypertrophy the murmur may be heard all over the chest and even to the top of the head. With a murmur of any intensity the first sound is usually absent, but it is very variable and in many instances of relative insufficiency the first sound is well heard. The second sound at the base is greatly accentuated, particularly to the left of the sternum over the region of the pulmonary artery. With failing compensation there may be a disappearance of the heart murmur and the condition of delirium cordis with a confusion of sounds.

The pulse in mitral insufficiency in the stage of compensation may be quite regular, but in the endocarditic group in children and in adults irregularity is almost always the rule. For years it may persist without any sign of cardiac weakness and with a normal blood pressure, and even when the pulse is very small and extremely irregular the patient may feel no inconvenience whatever.

FIG. 21

Pulse and respiration curve in mitral regurgitation (uncompensated). The pulse curve shows hyperdicrotism due to a low arterial blood pressure and marked irregularity of rhythm.

Diagnosis.—The recognition of mitral insufficiency is, as a rule, very easy, but it is not always so easy to determine the type of the disease. The endocarditic form in children accompanied with great dilatation and hypertrophy, and often with other valvular lesions, presents no difficulty. Nor in adults with the triple manifestations of a dislocated apex beat, a loud, rough, systolic murmur, and a greatly accentuated, pulmonic sound is there any real difficulty. In the hypertrophied heart of chronic Bright's disease, in myocarditis from whatever cause, and in the relative insufficiency of anæmias and toxæmias, it may be very difficult to determine whether there is an actual lesion of the valve or not. Usually the murmur in these cases is less intense, and shows marked changes in varying the posture of the patient. It may be present in the recumbent, absent in the erect position, and it may disappear entirely as the general condition improves, or as the dilatation of the heart subsides under the use of digitalis.

Prognosis.—Among valvular lesions it is at once the worst and the best. With the endocarditis of children, insufficiency may quickly reach a grade beyond the powers of compensation. On the other hand, a slowly induced insufficiency combined with a moderate degree of narrowing may become stationary, the edges of the valves calcify, the heart hypertrophy is well maintained, and the patient may live a long and useful life without any serious

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discomforts. It may be said that, as a rule, in children under ten the prognosis is bad, more particularly as they are apt to have recurring attacks of rheumatism, and the condition is not so much a valvular lesion as a general carditis. The older the individual at the time of the onset of the endocarditis the better is the prospect. The arteriosclerotic variety may not diminish the expectation of life. Indeed, it often happens that the discovery of a mitral bruit, at examination for life insurance, promotes longevity. Warned to be cautious, the patient takes better care of himself and avoids so far as possible stress and strain. In the cases of relative insufficiency the prognosis depends much more on the condition with which it is associated than on the valvular leak.

STENOSIS OF THE MITRAL ORIFICE.

Etiology and Pathological Anatomy.—The disease is most frequent in females. In 80 cases noted by Duckworth, 63 were in women. Of 196 cases at Guy's Hospital collected by Samways, 107 were females. In the Edinburgh Hospital statistics of 1914 cases of valvular disease, 304 were mitral stenosis alone, 231 were mitral stenosis and insufficiency, and 26 were mitral stenosis with an aortic lesion. The stenosis is frequently not present alone and insufficiency in some grade is a very common accompaniment. In fact, it may be said that the classical malady described in text-books and monographs as mitral insufficiency is almost always associated with some degree of stenosis, while mitral stenosis, except in a few rare instances, always permits of regurgitation. Etiologically, there are three groups of cases: (1) Those which follow an acute endocarditis. This is the most common form, and it occurs in the young and particularly in young girls. Rheumatic fever is the dominant factor, and next to it chorea. Of 140 cases of chorea examined at a period of more than two years subsequent to the attack, 72 had signs of organic disease of the heart, and 24 of these presented the physical signs of mitral stenosis. Scarlet fever, measles, and whooping-cough may be responsible for a few cases. It has been claimed that tuberculosis plays a certain role, but for this there is not much evidence. As to the influence of mitral stenosis on pulmonary tuberculosis there is much difference of opinion. The studies of Tileson[1] suggest that patients with mitral disease have a relative immunity to tuberculosis, and if it be present the pulmonary disease is mild with a strong tendency to cure. In a second small group of cases the stenosis is the result of a primary sclerosis of the valve with thickening and adhesion of the edges, shrinking of the chordæ tendineæ, with widespread atheromatous changes in the substance of the valve and in the mitral ring itself. It is not always easy to determine whether or not these changes have been initiated by an endocarditis, but this group occurs at the older period of life and in men as well as in women. Newton Pitt has pointed out the frequency of association with chronic interstitial nephritis, 33 cases in 542 autopsies. Lastly, there is an important group of cases met with almost exclusively in women, in which no positive factor can be determined. The cases are usually latent, found accidentally, and the condition may persist for many years without causing any symptoms. In adult women, in whom this

[1] *Journal of the American Medical Association*, 1908, vol. l, p. 1179.

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form is most common, one is almost always safe in putting the interrogative negatively—you have not had rheumatism. Some have thought that this form may be congenital, but this is unlikely, as it is rare to meet with lesions of the mitral valve during fœtal life or immediately after birth.

A functional or spasmodic stenosis of the mitral is spoken of, due either to spasm of the sphincter muscle or of the papillary muscles. The cases have been described in hysterical patients, and in anæmic and chlorotic subjects.

Anatomically, there are two forms, the pure or membranous, in which the left auriculo-ventricular ring is surrounded by a thin membrane representing the fused valve segments, perforated by a narrowed orifice which admits the tip of the little finger. The membrane is a little thickened, but it is pliable, the edges are smooth and may be readily placed in apposition, so that it is possible during life that the valve has been competent. These are the cases of what the French call *pure* mitral stenosis, and it is this form more particularly that is met with in women in whom no history of rheumatism or other etiological factors can be found. From the auricle this form presents a remarkable funnel shape. In the other variety the valve segments are greatly deformed, the chordæ tendineæ thicken, and with the irregular calcified excrescences with atheromatous plates the whole valve and ring are converted into a rigid mass, in the middle of which there is a linear slit or a rigid orifice that admits the tip of the thumb or index finger. The heart itself is not greatly enlarged, and may not weigh more than fourteen or fifteen ounces. In elderly persons the organ may, indeed, look small. The left auricle, as a rule, is greatly enlarged, and may hold several hundred cubic centimeters of fluid. Normally, the capacity in under 50 cc. Cases have been reported in which it has held 500 or even 650 cc. The appendix is usually greatly enlarged. The endocardium is very opaque, and when the dilatation is extreme the walls are very thin and fibrous. In the early stages, as Samways pointed out, the hypertrophy of the auricular walls is very marked.

The chambers on the right side are much enlarged, the ventricle contrasting in a remarkable way with its fellow; indeed, the apex of the heart may be made up entirely of the right ventricle. While this may be said to be the rule in mitral stenosis, there are some instances in which this contrast is not so striking, and the left ventricle may also be hypertrophied. The right auricle is greatly enlarged and the tricuspid orifice is much dilated.

Pathological Physiology.—Much of what has already been said of mitral regurgitation is true also of mitral stenosis. An increase of auricular pressure occurs at the end of diastole leading to stimulation and later to hypertrophy of the auricular muscles. Increase in auricular pressure from further obstruction at the valves causes such stretching of the muscle that increased action assisted by hypertrophy is not able to overcome the additional pressure. The orifices of the pulmonary veins now remain open during auricular systole, the pressure gradient in the pulmonary vessels becomes less steep and hypertrophy and increased action of the right ventricle follows as the result of the increased power required to empty the right ventricle. Mackenzie has recently put forward a view of the cause of the irregular pulse of mitral stenosis, which from both clinical and postmortem evidence is highly probable. He has noticed that when the crescendo murmur of mitral stenosis fails or is replaced by a low-pitched murmur, the irregular pulse

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appears; moreover, at the same time the evidence of the contraction of the left auricle fails. In several cases that he has observed over many years, the evidence of normal regular contraction of the auricle—a wave in the jugular pulse, a wave in the cardiograph, and a presystolic crescendo murmur—has not been present with an irregular pulse, or, as Mackenzie calls this particular form of irregularity, the *disorderly* pulse, from the absence of any rhythm in its irregularity. In one case drawings of the heart compared with the normal, show enormous dilatation of both auricles. The explanation given is that the auricular muscle has become so stretched that the normal impulse stimulating the ventricle to contraction, which comes from the entry of the great veins into the right auricle, is unable to reach the ventricle owing to the condition of the muscular fibers, and that the rhythm of the heart is now governed by that part of the conducting system of fibers (Tawara's Knoten) which lies nearer the ventricle and is not under such unfavorable conditions. In mitral stenosis the left auriculo-ventricular orifice is narrowed, hence, unless the auricular muscle is particularly strong, the ventricle does not receive as much blood as it should normally. This is especially so in the severer forms of stenosis. There is, therefore, no tendency to a dilatation or hypertrophy of the walls; in fact, with less inflow into the ventricle the cavity tends to become smaller and the bulk of the muscles less. In animal experimental stenosis, produced either by constriction of the auriculo-ventricular groove by a ligature or by introducing into the auricle a distensible balloon, the pressure in the systemic arteries falls, that in the left auricles and pulmonary artery rises. The blood pressure in man is not abnormally low; in fact, the same feature as has been noticed in mitral regurgitation may be present—namely, a very small pulse with a blood pressure slightly above normal. With good compensation there is but little departure from the normal, and when irregularity sets in the maximum pressure varies considerably—in one of Hensen's cases from 105 mm. to 140 mm. Hg.

Symptoms.—Latency may be said to be the special feature of the disease. At a busy clinic not a month may pass without meeting the most typical physical signs in a person who has had no symptoms whatever. Even narrowing of a shirt-buttonhole size may be present with nothing more than slight shortness of breath on exertion. In other instances the patient for years has irregularity of the pulse and is short of breath on exertion. We must recognize a large group of cases in adults in whom the lesion is well borne for an indefinite number of years. In children it is different, particularly in the cases that follow rheumatic fever. There is very often failure of development. They remain feeble, the breath is short, they are anæmic, and there is a liability to fresh attacks of endocarditis. Many patients present for years a slight cyanosis, more particularly of the cheeks and of the ears, and are liable to have recurring attacks of bronchitis in the winter.

The symptoms of cardiac breakdown are very much the same as in other forms of valvular disease. The irregularity becomes more marked, œdema of the feet and ankles occur, the breath is short and the signs of stasis are present in the viscera. Brisk hæmoptysis may occur sometimes with relief. Among unusual symptoms is paralysis of the left recurrent laryngeal nerve by pressure of the enlarged left auricle. This, in connection with a wide area of impulse in the second, third, and fourth left interspaces may lead to the

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diagnosis of aneurism. The senior writer has seen two cases of this kind, and others are reported in the literature.

Accidents in the disease are common, such as sudden attacks of congestion of the lungs and acute infarcts with hæmoptysis. Sudden death in an acute cardiac failure may occur. Embolism is very common, the embolus being either a fragment of a clot from the dilated left auricle, or more frequently a fresh vegetation is whipped off from the orifice of the valve and plugs the left Sylvian artery, causing right hemiplegia with aphasia. In other instances there is embolism of the peripheral arteries. In rare cases widespread thrombosis may occur.

Physical Signs.—Inspection.—Nothing may be noticed. The apex beat may be in the normal situation and the precordia does not suggest a valve lesion. The heart, indeed, may appear to be smaller than normal. In other cases the apex beat is moved an inch or two to the left, the impulse is more forcible and there is marked pulsation in the parasternal line and the lower sternum. In children the precordia usually bulges and there is marked pulsation in the interspaces along the left margin of the sternum from the second to the fifth or sixth. In advanced cases the pulsation of the enormously enlarged heart may be seen to the right of the sternum, but in pure mitral stenosis the hypertrophy of the heart rarely reaches the degree seen in insufficiency.

Palpation.—In a considerable proportion of all cases, when the lesion is well compensated, the diagnosis may be made by palpation alone. At the apex is felt a purring thrill—the *frémissement cataire*. It is limited in area, rarely felt above the fourth rib, most marked during expiration, occasionally only brought out after exertion. Coinciding with the diastole of the ventricle, it may be felt to extend throughout the whole period, or it is only in the latter part, rising crescendo-like toward the end and terminating in the sudden, sharp shock of the first sound. The localization, the occurrence in diastole, the purring, vibratory quality, and the abrupt termination in the first sound, form a quartet of signs that rarely lead us astray. As the disease advances and a stage of decompensation is reached the thrill may disappear.

Percussion.—In the early stages there may be no increase in the area of cardiac dulness. With the increase of the left auricle, the flatness to the left may be increased, but the great enlargement is in the right ventricle with extension of the dulness to the right of the sternum. The absolute cardiac flatness reaches high on account of the enlargement of the conus arteriosus. The great dilatation of the left auricle may compress the upper lobe of the lung, and the area of deep dulness may be much increased upward in the third and fourth interspaces. But the auricle itself rarely comes in contact with the chest wall. This enlargement of the auricle is well seen with the fluoroscope.

Auscultation.—In compensated cases there is heard in diastole a rumbling, vibratory, or purring murmur, usually increasing in intensity and terminating abruptly in a loud, snapping, first sound. The special features of the murmur of mitral stenosis are: (1) Its limitation: the bell of the stethoscope may cover the region in which it is heard. (2) The quality: vibratory, grating, or a low, echoing rumble; with the exception of the rare instances of tricuspid stenosis, this quality of murmur is only heard at the mitral orifice. (3) The sharp, valvular, first sound. There are many modifications and changes.

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In the early stages of the disease there may be nothing more than a slight echoing rumble, and it is only on exertion that the characteristic murmur is brought out. Its position in diastole is variable. It may occupy the entire period, rising crescendo-like toward the close. It may be purely presystolic, occupying only the terminal portion and running directly up to the sharp valvular first sound. In other cases it is mid-diastolic, and the perceptible short interval separates it from the first sound. No other murmur may be present. A very soft systolic may be heard in some cases, with very slight extent of propagation. When decompensation is present the typical presystolic murmur may disappear and a loud systolic is heard.

The state of the sounds of the heart in mitral stenosis are of exceptional interest. As already mentioned, the shock of the first sound is extraordinarily forcible. Except in certain neurotic states, no such snapping sound is felt at the apex. On auscultation, too, it is remarkably intense, and instead of a dull, thudding sound, it is of a flapping, valvular, even of an amphoric, ringing quality. So intense may it be that we meet here one of the few conditions in which the heart sounds are audible at a distance from the chest wall. It is common enough to hear the first sound a few inches away, but twice it has happened in my experience to hear a clear, bell-like first sound as I sat at the bedside of the patient. In one case Dr. Blake, of Baltimore, measured the distance, and found it a little over six feet. Naturally, this

FIG. 22

Pulse tracing. Mitral stenosis.

loud, ringing sound is propagated to the back. The second sound may be well heard at the apex, sharp and accentuated, increasing greatly in intensity as the stethoscope is passed toward the second left interspace. Here it is often reduplicated. In later stages the second sound may disappear at the apex, while it is loudly audible at the base. In the stage of decompensation, with great irregularity and dilatation of the heart, the characteristic physical signs may disappear. Time and again the diagnosis of mitral stenosis is made for the clinician by the pathologist. A week's rest in bed with the use of digitalis may serve to bring back a presystolic murmur. In other instances a murmur of typical quality and a first sound of amphoric timbre may disappear and be replaced by a loud mitral systolic. An acute illness, a period of debility from any cause, may cause the murmur to become very feeble or even to disappear. In such instances there may be nothing but a faint diastolic rumble, which is changed into a more definite murmur on exertion.

In uncomplicated cases no murmurs are heard at the aortic area. The first sound is usually very feeble in comparison with the second.

Diagnosis.—No valve lesion is more readily recognized than mitral stenosis. One has always to bear in mind that when the terminal stage is reached, and the patients are admitted with delirium cordis, the murmur is no longer present, and the diagnosis may be perhaps only suggested by the sex of the patient and by the fact that there is a somewhat snapping first sound. A murmur with the same quality during diastole at the apex

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is heard in aortic insufficiency, known as the Flint murmur, and has already been discussed. In tricuspid stenosis a rumbling presystolic murmur is heard of maximum intensity over the body of the heart. In the conditions in which the senior writer has heard it, mitral stenosis has always been present as well. And lastly, in a considerable number of cases of pericardial adhesion a rumbling apical murmur is heard in diastole. It rarely has the peculiar limited localization nor does it end in a snapping first sound.

TRICUSPID INSUFFICIENCY.

Etiology.—There are two groups of cases, one the result of organic disease of the valve cusps, the other relative or functional incompetence from dilatation of the tricuspid ring due to lack of tone (muscular insufficiency) in the right ventricle.

1. Organic disease follows rupture, endocarditis, or a chronic fibrosis of the segments. (*a*) Rupture of the valves or of the chordæ tendineæ may follow a blow on the chest or an excessive effort. (*b*) The endocarditic form occurs in the acute infections, more particularly rheumatic fever. (*c*) The etiology and appearance of fibrosis of the tricuspid valves are similar to those of the mitral.

Because of the lessened strain put upon the tricuspid valve in adult life, inflammation and degeneration of its leaflets are much less frequent than in the mitral valve. Probably also because of the greater tension which has to be borne during fœtal life, the relative frequency of endocarditis in the right and left sides is reversed. Congenital endocarditis is almost always confined to the right side of the heart. In adult life affections of the tricuspid are rare. By far the most frequent cause is rheumatic fever, and when present on the right side endocarditis is, in the majority of cases, associated with the same process of the mitral valve, of the aortic valve, or of both. In addition, affections of the valve have been determined to be due to the pneumococcus, gonococcus, tubercle bacillus, streptococcus, and typhoid bacillus. Gummatous change of the valves has been described. As a sequence of other valvular disease, mitral or aortic, degenerative changes may cause insufficiency. Malignant disease is extremely rare.

2. Relative insufficiency arises in a large number of conditions. The fibrous ring which surrounds and supports the auriculo-ventricular orifice is liable to become stretched, and at the same time the muscle of the ventricle suffers distention. This means a larger orifice for the valves to close, and as the chordæ tendineæ cannot elongate, the orifice remains open, its cusps not being able to meet in close apposition. It is a question whether the inability of the muscle to lessen the ventricular cavity to its normal size in systole does not play a large if not the chief part, for if at the height of systole the cavity were no larger, it is conceivable that even with a dilated ring no regurgitation might occur; but if with a dilated ventricle the degree to which the ventricle can contract be lessened, then the cavity is fuller at the end of systolic than normal and the valve cusps are not properly approximated.

The important part played by the muscle of the ventricle was put forward in a masterly way by T. Wilkinson King[1] in 1837, and the following

[1] Safety Valve Action in the Right Ventricle of the Human Heart, *Guy's Hospital Reports*, London, 1837, ii, 104.

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account which he gives of the anatomical relations of the tricuspid valve and its connection needs no revision. "The right auriculo-ventricular opening is oval; and to its circumference the membrane of the tricuspid valve has attachment without any distinct interruption; whilst its floating border depending into the ventricle is deeply fissured, so as to form three or more scalloped or angular curtains. And it appears from careful examination that the united areas of these valvular portions are scarcely more than equal to the mean extent of the oval opening. One of these curtains (which, not being movable, I have called fixed) occupies the left margin of the aperture in apposition with the solid wall, from which arise all the cords that serve to secure the free edges and ventricular surface of the fixed curtain. These cords are of such a length as scarcely to allow the curtain to rise into the plane of the oval opening in the natural play of the valve, and being destitute of muscular columns, cannot by any possibility set the valve in motion, or serve any other purpose than that of preventing too great a reflex of the curtain itself. A second curtain (the anterior) is attached at the anterior and right edge of the opening, having one free border forward and another backward in the ventricle. Each border has its proper set of cords: the anterior or upper set having their insertion into a mere nipple of muscle on the solid wall in the direction of the pulmonary artery; and the inferior or posterior are as invariably collected with numerous others into the summit of a muscular column whose base is inserted into the thin right or yielding wall of the ventricle near its centre, where also is attached, almost as regularly, another muscular band which stretches across the cavity between the two walls. This band may have an average length of six or seven lines and a circumference of three or four. It seems calculated to limit distention, and therefore I have called it the moderator band of distention. The third curtain or fold of the valve (the right) is situated on the right side of the aperture posteriorly, and has little or no connection with the inner or left edge of the opening. In extent and figure it varies considerably, and it rarely forms one single scallop, but is frequently fissured so as to form two or three, more or less complete. Its cords are accordingly arranged in two or more sets, the greater part of which are attached by the intervention of muscular columns to the outer yielding wall at a considerable distance from the solid wall, and usually without any transverse bridge or moderator band.

"The construction . . . I have described in connection with the yielding, *i. e.*, the outer wall of the ventricle, constitutes the main peculiarity of arrangement and action in the tricuspid valve, the great extent, thinness, and feebleness of the yielding wall rendering it liable to the distending influence of venous accumulation in various degrees; the curtains being three, and each one tethered to that part of the ventricular parietes immediately beneath itself (but most extensively to the yielding wall), by the intervention of columns whose passive effect is to produce a retraction of the curtains in proportion to the distention, and whose active contractions serve under dilatation to augment the valvular retraction, or rather to maintain it at its height during the imperfect systole . . . and further, the orifice itself, depending on the yielding wall, may admit of some relaxation and thus assist to produce regurgitation."

Following these anatomical observations, King performed several experiments on human hearts in which no disease could be detected. By putting pressure into the left ventricle, it was easy to effect a complete and adequate

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closure of the mitral valve, and only with very considerable pressure did the escape of water into the auricle occur. In the right ventricle, however, no position of the heart and no variation of the conditions were sufficient to prevent the escape of a tape-like stream of water into the right auricle, unless the walls of the ventricle were at the same time compressed by the hand. King suggested the effect of cardiac tonicity on the production of a complete valvular ring, and demonstrated it by showing in a heart, in which rigor mortis appeared after removal, that the deficiency of the valve became almost negligible.

Relative tricuspid insufficiency, therefore, is really one caused by affections interfering with the muscle of the right ventricle, and its causes may be summarized as follows:

(*a*) Mechanical dilatation, due to an increase in pressure in the ventricle at the beginning of systole, may be caused by overexertion, asphyxia, and abnormal fixation of the chest wall, as in some forms of labor. Other causes are those which oppose an obstruction in the pulmonary circulation—chronic bronchitis, sclerosis of the lung arteries, bronchiectasis, chronic fibroid disease of the lungs and pleura, and disease of the mitral valve. The ease with which this dilatation is brought about may be shown by the fact that by holding the breath for one minute the right border of the heart, as determined by deep percussion, travels to the right at least one inch.

(*b*) Dilatation of the right ventricle, the result of a failure in muscular nutrition, is observed in all forms of local cardiac disease, myocarditis, pericarditis, and gummata of the heart. Of general diseases, the most important are malnutrition, as in diabetes, cachexia from neoplasms, debility from atonic conditions of the stomach, and in the anæmias, especially in pernicious anæmia. Prolonged and high fever tends to an enfeeblement of the cardiac muscle and to insufficiency of the tricuspid valve.

Pathological Physiology.—*Mutatis mutandis*, what has been said of mitral regurgitation applies here. With insufficiency the first stress is thrown upon the right auricle, which, by hypertrophy and compensatory dilatation, opposesa mechanism against the effects of regurgitation. When the regurgitation becomes greater and the cavity of the auricle has to dilate to such an extent that it cannot exert sufficient force on the contained blood, the muscle bands by which the orifices of the veins are closed during systole are stretched and become ineffective. There is then during systole of the ventricle a continuous column of liquid from the ventricle into the veins without the opposition of any valvular mechanism. It is obvious, then, that the condition of the blood in the venous system from the clinical aspect is of considerable importance. With very few exceptions, a jugular pulse may be seen in every normal person, if not in the upright, in the recumbent position, or with the head slightly lower than the feet, when the veins of the neck become fuller and pulsation can be observed. In fat persons it may be extremely difficult to detect, but even in these a tracing can be obtained. With little practice, with or without the aid of tracings, three waves can be detected in the supraclavicular triangle under proper conditions as regards light. First, a wave appearing slightly before the impulse of the heart at the apex beat, due to the pulsation of the right auricle; secondly, a wave which is synchronous with the beat in the carotid artery, as felt higher up in the neck; and thirdly, a wave occurring immediately after systole of the ventricle (the ventricular wave). The significance of this last wave is not certain.

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Mackenzie has shown, by tracings of this pulsation taken in numerous cases of heart disease, that when the right side of the heart is at fault, as in failure from mitral disease, a change often comes over the jugular pulse in which the auricular wave diminishes or disappears and the ventricular wave increases in size and occurs earlier in relation to the ventricular output than in normal cases.

The transition is shown diagrammatically in Fig. 23. When the alteration is fully developed there is only one large wave in the jugular pulse, which for the most part is ventricular in time. Mackenzie calls this form of venous pulse the "ventricular" form, and has taken it to mean tricuspid regurgitation. This view has recently received striking confirmation by Rihl,[1] who, by making an artificial lesion of the tricuspid valves in rabbits, finds that according to the severity of the lesion there are two sharply defined forms: first, that in which the regurgitation is slight and the venous pulse shows no change from the normal; and, secondly, that in which the venous pulse is of the ventricular form. We must suppose that in the former condition the auricle of itself can compensate for the regurgitation without undue stretching of its walls by the regurgitated blood. This is confirmed by finding that in these less severe forms, stimulation of the vagus, the beginning of asphyxia, and so on, which in the normal animal are without effect on the jugular pulse, in the mutilated animal, produce a ventricular venous pulse. The effects of experimental tricuspid insufficiency in rabbits have been investigated by Stadler,[2] who finds a dilatation and hypertrophy of the right auricle and ventricle and some diminution in the weight of the left ventricle compared with normal rabbits. This corresponds with the observation made in the rare cases in man in which the tricuspid valve alone is affected.

FIG. 23

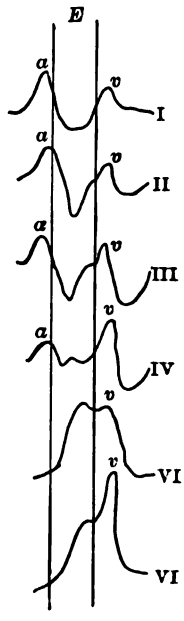

Diagram to show the transition from the normal venous pulse to the ventricular form, *i. e.*, in tricuspid insufficiency. *I*, is the normal venous pulse from which the *c* wave, occurring between *a* and *v*, probably due to the carotid artery, has been omitted; *a*, auricular wave; *v*, ventricular wave, whose significance in the normal venous pulse is doubtful. *E*, period of outflow into the pulmonary artery. (After Mackenzie.)

Morbid Anatomy.—The heart in pure tricuspid insufficiency has certain distinctive features. The right auricle is dilated and globular, the right ventricle is more prominent and fuller than normal, and appears to be creeping round the left ventricle. The amount of distention of the right auricle and ventricle depends on the rapidity of onset of the lesion or whether organic disease is present in the valves, the condition of the muscular walls, and so on. The best example of a pure functional tricuspid insufficiency is

[1] *Verhandlungen des Congresses f. innere Medizin*, 1907.
[2] *Deutsch. Arch. f. klin. Med.*, 1905, lxxxiii, p. 71.

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to be seen in death from asphyxia, in which the right heart, especially the auricle, is enormously dilated. When organic disease of the valve is present, the ventricle and auricle have had time in part to oppose a certain amount of hypertrophy against the valvular defect, consequently in the organic cases the enlargement is not so great and is made up of hypertrophied muscular wall in addition to the dilated cavity.

The proof of insufficiency of the valve is easily made by directing a stream of water from the auricle into the ventricles and then pressing the right ventricle with the palm of the hand, avoiding any pressure that will cause an approximation of the attachments of the chordæ tendineæ to their insertion on the valve cusps. If the valve is incompetent, a stream of water will regurgitate into the auricle. The condition of the valve in relative or functional insufficiency is normal, the cusps being thin and the chordæ tendineæ not thickened or shortened. In the case of organic insufficiency the state of the valve will vary according to the cause. The valve may have been ruptured either by effort or by a blow. A recent endocarditis takes the form of small excrescences or larger irregular masses attached to the valves. If, on the other hand, there is chronic fibrosis, the cusps are thickened, glistening white or yellowish, and the chordæ tendineæ thickened and shortened. The mural endocardium in the chronically dilated cavity is always thicker than normal. On account of the pressure to which they have been subjected, the veins opening into the right auricle are dilated, their walls are slightly thicker than normal, and this thickening extends into the jugular and the subhepatic veins.

The liver, spleen, and kidneys all show the chronic cardiac congestion described under mitral disease; in fact, these appearances in the two diseases are due to the failure of the right side of the heart. The lungs in experimental animals are dry and bloodless, and the same has been noted in pure cases of tricuspid insufficiency in man.

Symptoms.—The chief complaint of the patient is breathlessness on exertion, and if the lesion is uncompensated there is quickened breathing or orthopnœa, even at rest. The slightest exertion causes dyspnœa and a sudden sense of oppression in the chest. In advanced cases orthopnœa is marked. Pain is not a prominent symptom. It most frequently occurs in relation with an enlarged liver whose capsule is stretched, and consequently the pain is felt on the right side of the abdomen. The digestion is always faulty and the appetite is lessened or absent. Distention of the abdomen, either in relation to meals or not, is common, relieved sometimes by eructations or by purgatives. Œdema of the legs and feet sets in early and is of the usual type, being less evident after a night's rest in bed. Ascites may be present even before any œdema occurs.

Physical Signs.—The facies of the patient with marked regurgitation is one of intense cyanosis. The whole surface of the skin is a livid blue color, the extremities, such as the ears, the tip of the nose, and the fingers being of a deeper color than the rest of the skin. The lips are a violet blue. The sclerotics are darker than normal and of a subicteric tint. The visible veins, such as those of the temple, neck, arms, and chest, are dilated and prominent. If noticed carefully, two types of pulsation may be distinguished in those of the neck: first, rhythmical emptying and filling; secondly, pulsations synchronous with the heart beats, best seen in the right supraclavicular triangle outside the sternomastoid, over the spot where the external

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and internal jugular veins enter into the subclavian. In fact, the jugular sinus may be so dilated as to form a rounded swelling just above the clavicle. The pulsations may extend over the veins of the shoulders and mammary regions and down the superficial veins of the arm and the elbow. Inspection may show a large area of precordial pulsation, especially noticed over the lower end of the sternum and in the epigastrium. In cases with a marked pulsation in the jugular veins, pulsation in the liver can usually both be felt and mechanically recorded.

The apex beat is diffuse and extends outward to the left as far as the nipple line or farther into the left axilla. On palpation sometimes a light systolic shock may be perceived. On determining the limits of pulsation the area is found to lie over the lower end of the sternum and along a strip stretching from the sternum to the apex beat, an area corresponding to the right ventricle. On percussion the transverse dulness is increased and stretches more to the right than normal. Schwartz has recently suggested that the deep cardiac dulness in relative tricuspid insufficiency extends farther to the right than in organic deficiency of the valve, and he suggests that dulness extending beyond three fingers' breadth to the right of the sternum—it sometimes extends as far out as the right nipple line—should be regarded as almost certainly due to relative tricuspid insufficiency, because the stretching of the ventricular muscle must be great in order to produce insufficiency. Relative tricuspid insufficiency can easily be demonstrated on a healthy person if the breath be held for about one minute. If the right border of the cardiac dulness be percussed out before the experiment, it will be found immediately after holding the breath for that time to have extended outward for about one inch.

On auscultation a systolic murmur can usually be detected in the cardiac area. It may be rough, especially if the insufficiency is the result of endocarditis. On the other hand, if the insufficiency is relative, it is faint and delicate. Tricuspid systolic murmurs are more superficial than mitral; their pitch is higher and their duration longer. The point of maximum intensity is over the sternum and to the left rather than to the right. It may, however, be heard to the right of the sternum, which can hardly ever be done in mitral insufficiency.[1] The *x*-rays, as has been pointed out by Bonninger,[2] may be used as a means of distinguishing certain heart lesions. In a case of pure tricuspid insufficiency the maximum pulsation is toward the right border of the heart, and the extended pulsation of the left auricular region, so characteristic of mitral failure, is absent.

Diagnosis.—From a careful observation of the jugular pulsation in the neck and careful auscultation over the precordia, there is seldom much doubt as to the presence or absence of tricuspid regurgitation. The veins of the neck show in proportion to the deficiency of the valve a pulsation which is synchronous with the ventricular systole. If by observation the time of the most prominent wave is not easy to determine, then a tracing of the pulsation, especially if combined with an apex tracing, will determine exactly the time of the jugular pulsation. To distinguish the murmur of mitral regurgitation from that of tricuspid regurgitation is by no means always easy. Mitral systolic murmurs may be loudest at almost any point to the

[1] Heitler, *Deutsch. med. Woch.*, 1897, p. 106.
[2] *Deutsch. med. Woch.*, 1907, p. 333.

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left of the sternal border below the second interspace; less frequently they have their maximum intensity over the ensiform process. The tricuspid murmurs are soft, blowing, rarely rough, more superficial, shorter, and usually higher in pitch. The loudest can be heard over the entire sternal area, generally plainest opposite the fourth interspace, and more distinct over the middle and left half than toward the right side of the sternum. Less frequently they are heard best over the lower half of the sternum. The conduction of the murmur may be either to the right or to the left, to the left better than to the right. Faint murmurs are not heard above the third rib.

It is important to determine whether the incompetence is relative, due to stretching, or from organic change in the valves. The following points are suggested by Schwartz:[1] With a positive venous pulse and a percussion dulness of the right border of the heart not extending beyond three fingers' breadth to the right of the right sternal edge, an organic lesion of the tricuspid is the more probable. If, on the other hand, the right cardiac dulness extends farther to the right than three fingers' breath, a relative insufficiency is more probable, because the valves are insufficient by the stretching of the muscle, which may be so great as to make the right border extend by percussion to the right mammillary line. Another important point is that in organic insufficiency after the reëstablishment of compensation the positive venous pulse remains, while in relative insufficiency the positive venous pulse is replaced by one in which the auricular wave becomes more prominent.

Prognosis.—In those cases in which the deficiency is due to organic disease the prognosis is always grave, for only very rarely is it unaccompanied by disease elsewhere in the heart and because any failure of the right ventricle is immediately followed by symptoms of heart failure. In relative tricuspid insufficiency the prognosis depends more on that of the cause of the insufficiency than on the valvular defect itself.

TRICUSPID STENOSIS.

Etiology.—Tricuspid stenosis, a chronic disease due to fibrosis of the valve, may follow an infective process or be the result of a primary degeneration of the tissue. The character of the infection is often doubtful, and we are therefore driven to examine clinical in conjunction with postmortem records. Leudet, in 1888, collected a series of 114 cases. Herrick, in 1897, added 40 cases. Newton Pitt, in 1899, collected from the records of Guy's Hospital a total of 87 cases out of 12,000 postmortem examinations, and Wardrop Griffith, in 1903, studied 19 cases from the portmortem records of the Leeds Infirmary and the specimens in Yorkshire College Museum. In a majority of cases rheumatic fever was the most important single factor. In the 173 cases of Leudet, Herrick, and Griffith, 59 had a definite history of rheumatism or chorea, *i. e.*, 34.9 per cent. In Newton Pitt's series the percentage is much greater, 62.06 per cent.; and if the cases with a history of vague rheumatic pains be admitted, the proportion becomes somewhat larger. Of other infections causing tricuspid stenosis we have no certain

[1] *Verein f. innere Medizin*, Abstract in *Deutsch. med. Woch.*, 1903, v, p. 318.

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knowledge. Syphilis is mentioned as an antecedent in one of Griffith's cases. Two cases have been reported in which a pedunculated ball-like tumor projected down from the auricle and partially occluded the tricuspid valve.

Females are affected much more frequently than males; in a total of 260 cases collected by Leudet, Herrick, Pitt, and Griffith, 179 were females, 63 were males, and in 15 the sex was not mentioned. The age incidence at death is well shown from Pitt's series of cases: between eleven and twenty years, 16 cases; between twenty-one and thirty years, 31 cases; between thirty-one and forty years, 22 cases; between forty-one and fifty years, 10 cases; between fifty-one and sixty years, 3 cases; between sixty-one and seventy years, 2 cases.

The association of other cardiac lesions is a special feature in tricuspid stenosis; thus, in the 173 cases collected by Leudet, Herrick, and Griffith, the following valvular lesions were found: stenosis of the tricuspid valve alone in 12 cases; stenosis of the tricuspid valve with mitral stenosis in 97 cases; with pulmonary stenosis in 3 cases, with lesions of the aortic and mitral valves in 58 cases, and with lesions of the mitral and pulmonary valves in 3 cases.

Pathological Physiology.—A pure stenosis gradually increasing in degree causes an overfilling of the right auricle, and by stretching the muscle of the auricular wall, this leads to more vigorous contractions and is followed by hypertrophy of its muscular wall. As the stenosis increases, the auricle, even although hypertrophied, will not be able to empty its contents during systole, and consequently the cavity enlarges. The closure of the veins which open into the right auricle is probably effected by the muscular bands, especially those which lie around the venous openings. In the dilated auricle these are unable to contract properly and in the veins remain open. Consequently, at each auricular systole a regurgitant wave, presystolic in time, travels up and distends the vein. The hypertrophy causes a greater wave than normal. With increase in the stenosis the auricle tends to become so dilated that its power, even although hypertrophied, is inadequate to expel more than a fraction of the blood into the ventricle. The auricular pulsation then fails, and with it the transmitted pulsation in the jugular veins. These two conditions correspond to two types observed clinically: first, the cases in which there is jugular pulsation in turgid veins, auricular in time; secondly, the cases in which, although the veins are turgid, no pulsation can be observed in them.

Morbid Anatomy.—The general appearance of the body is the same as that in death from chronic mitral disease with anasarca. The cyanotic tint is more marked than in other cardiac lesions. The pericardium has been found adherent. As tricuspid stenosis is so often associated with mitral stenosis, it is not always easy to say which anatomical features correspond purely to the former. If the heart be stuffed before being opened, the chief feature is a marked enlargement of the right auricle associated with a dilatation and a thickening of the walls of the superior vena cava and its branches. This dilatation may be sufficient to do away completely with the function of the valves, so that there is a continuous cavity from the venous system to the right auricle. This is well shown in one recorded case in which there was a continuous clot extending from the right auricle into the veins of the neck. The state of the right auricle depends upon the conditions of the circulation at the time of death; if this has occurred while the

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auricle by hypertrophic increase has been capable of propelling blood through the constricted orifice, the cavity of the auricle is large and its walls thickened by more layers of muscle fibers. But if the patient has lived a stage farther, the cavity is dilated and the wall of the auricle very much thinned, so much so that in areas as much as 5 cm. across, the auricular wall is composed of epicardium and endocardium alone. The rest of the muscular tissue of the auricle is proportionately thinned in these cases. The endocardium of the auricle, in consequence of continued back pressure, undergoes increasing thickening, and at death is much less transparent than in a normal right auricle. The tricuspid orifice is narrowed in different cases to different degrees; cases have been reported in which it scarcely admitted the little finger. The three cusps are so welded together and thickened that they are indistinguishable, except by comparison with their relations to the papillary muscles. The chordæ tendineæ are thickened and shortened. Other appearances have been described. In the case reported by Gairdner the orifice was blocked by a fibrinous ball attached to a point on the auricular wall. In another case reported by Philip,[1] large recent vegetations filled up the cavity. The right ventricle showed some enlargement of its cavity and thickening of its walls. In almost all accurately recorded cases some degree of mitral stenosis has been present.

The condition of the lungs varies, and in this regard also we cannot distinguish the effects of a tricuspid stenosis from those of a mitral stenosis. They are sometimes found to be dry on section, with only a small amount of hypostatic congestion at the bases and no marked œdema, sometimes markedly œdematous and congested with pneumonic consolidation at the bases, or with hemorrhagic infarcts. The liver, although presenting the appearance of chronic stasis, is not always enlarged; in fact, some livers have been distinctly below the average size (Stow's case). The edges are rounded, as would be expected from the chronic overfilling with blood under pulsation; the capsule is thickened, and on section the organ drips with very dark blood, showing a surface with the features of the "nutmeg" liver. A notable feature is the increase in connective tissue. Perihepatitis has been present.

Symptoms.—That a considerable degree of stenosis may not be productive of symptoms is shown by the history, reported by Gairdner, of a man who was under observation for ten years, led an active life during that time, and died at the end of the period from pneumonia. The symptoms of tricuspid stenosis are in the main very similar to those of tricuspid insufficiency, but they present certain important differences. Cyanosis may be present for a year or even longer before any other sign of cardiac failure. It is not of a very pronounced grade, nor so marked as that seen in extreme degrees of congenital heart disease, but is often sufficient to give trouble to the patient and to give occasion to remarks. A patient who was observed by Hirtz and Lemaire for two years was called by his fellows "l'homme bleu" without any suspicion of heart disease being present. Breathlessness is the most frequent complaint; it is more marked and comes on sooner than in lesions of the left side of the heart. Even very slight exertion, such as walking, may bring on severe dyspnœa. Other symptoms of heart failure differ in no respect from those in left-sided lesions, such as œdema, ascites, pain

[1] *Edinburgh Hospital Reports*, 1893, i, 235.

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in the right hypochondrium from the engorged liver, indigestion, constipation, and so forth. In certain cases anginal pain is complained of, which may pass down the left arm, occasionally down the right. It is often questionable in a given case which symptoms are due to the tricuspid stenosis and which to the frequently associated mitral stenosis. Gairdner's patient complained of the jugular pulsation in the neck. All patients in whom the cyanosis is marked complain of great susceptibility to cold. Of symptoms due to stasis in the systemic veins, œdema, ascites, jaundice, and petechiæ are frequent. Hæmoptysis, noticed in twenty cases in Newton Pitt's series, is probably due to the mitral stenosis.

Physical Signs.—The patient, as a rule, is cyanotic, the tint being most marked in the lips, nose, ears, and hands. The veins are dilated and may be specially noticed in the lower part of the neck. The jugular bulb may be dilated to such an extent as to produce an ovoid swelling, which may or may not show pulsation. If none is visible, it may often be brought out by getting the patient to sit or stand up. An important distinction between stenosis and insufficiency of the tricuspid valve lies in the form of the jugular pulsation; in the latter the type of the jugular pulse is ventricular, *i. e.*, the most prominent wave is systolic in time; in tricuspid stenosis the largest wave is the auricular, and hence presystolic. Mackenzie has pointed out this distinction, and, further, that the liver pulsation, which is a constant feature of these cases, shows a large wave also auricular in time. The narrowing of the tricuspid orifice protects the auricle from the overdistention due to a large regurgitant stream, while the overfilling of the chamber, from a diminished outflow through the contracted orifice, serves to stimulate the auricular muscle to vigorous action and hypertrophy. The auricular pressure forced into the veins in systole often causes so great a tension in the valves at the entrance of the internal jugular vein that an audible sound, auricular in time, is heard on auscultation over this area. When fulness without any pulsation is present, there is probably a paralysis of the right auricle from overdistention.

Inspection.—As, almost without exception, there is associated mitral stenosis, it is difficult to separate the signs due to tricuspid stenosis alone. The area of pulsation is greater than normal, the apex is usually localized with difficulty and is seen farther out to the left. Some pulsation is seen in the costosternal angle.

Palpation.—A thrill presystolic, sometimes systolic, in time can be felt, the presystolic having its maximum intensity over the lower end of the sternum.

Percussion.—The cardiac dulness is increased to the right and occasionally in the upward direction.

Auscultation.—In the majority of cases recorded there has been a rough presystolic murmur, not quite so harsh as that heard in mitral stenosis. The point of maximum intensity and its area of audibility differ in different cases, but it may be said generally that the maximum point is somewhere near the lower half of the sternum, and it is propagated radially from that point. Sometimes it is heard over the entire sternum, more distinctly to the left side, sometimes over the lower half of the bone. Occasionally the murmur is heard to the right. Polycythæmia is almost constant, and, as a rule, well marked, often 8,000,000 or 9,000,000 red cells per cubic millimeter. The fingers are frequently clubbed. If there is any cardiac

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failure, the urine contains albumin, and glycosuria has on rare occasions been noticed.

Diagnosis.—The reports of a large number of cases show that tricuspid stenosis may be mistaken for mitral stenosis, for tricuspid insufficiency, for congenital cyanosis, for pulmonary stenosis or deficiency of the septum of the auricles.

Considering the similarity of the symptoms in mitral and tricuspid stenosis, it is not surprising that the rarer lesion is occasionally overlooked. The points of distinction are as follows: The cyanosis in tricuspid stenosis is more marked and more constant; in mitral stenosis the cyanosis is more clearly associated with a loss of compensation and with stasis in the pulmonary vessels. If digitalis be given to a patient with mitral stenosis, the cyanosis, as a rule, lessens, but in a patient with tricuspid stenosis little if any effect can be noticed. A careful examination of the chest and neck should be made and attention paid to the following points: if the veins of the neck are full and pulsate with each auricular beat, tricuspid stenosis is more likely. In mitral stenosis with cardiac failure, insufficiency of the tricuspid would be produced and a positive, *i. e.*, systolic, *i. e.*, ventricular, venous pulsation would be produced. The precordia should be carefully palpated to determine the delimitations of any thrill that may be present. A presystolic thrill in the neighborhood of the apex suggests a mitral lesion; one more to the right, especially if its point of maximum intensity be felt on or near the sternum, suggests tricuspid stenosis. Careful auscultation, again, will sometimes show that a presystolic murmur present at the apex alters its character on being traced to the right toward the sternum, and with its altered character becomes more intense in that region. In a case recorded by Mackenzie the presystolic murmur produced at the tricuspid orifice could be heard over the whole of the lower two-thirds of the sternum and over a considerable area to the right.

Several cases are on record in which physicians of great experience have mistaken a tricuspid stenosis for insufficiency, even although repeated examination has been made for signs of tricuspid stenosis. It is well recognized clinically that mitral stenosis with loss of compensation may be at times difficult to recognize. This is also probably true of tricuspid stenosis. The mitral stenosis in the stage of loss of compensation is mistaken for mitral regurgitation; similarly the tricuspid stenosis with loss of compensation is mistaken for one of tricuspid regurgitation. To follow this a little farther, reference has been made in speaking of mitral stenosis to the work of Mackenzie and his suggestion that the disappearance of the presystolic mitral murmur is associated with the assumption of a disorderly rhythm and the disappearance of the auricular wave in the venous pulse. Mackenzie considers that the disorderly heart rhythm is due to the stretching of the primitive muscle tissue, increasing its excitability and causing it to act as the stimulus to the ventricular muscle instead of the normal impulse from the superior vena cava. An examination of the records shows that although in many cases a venous pulse has been noticed, recorded graphically, and proved to have an auricular wave, in others no pulsation of the veins of the neck has been seen. Cases, however, which have shown an auricular venous pulse have also had a regular pulse rhythm, a presystolic thrill, and murmur in some situation, which suggest a tricuspid rather than a mitral origin. It is suggested, then, that in those cases in which competent observers

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have diagnosed tricuspid regurgitation, insufficiency alone was indicated, the symptoms of stenosis having disappeared by reason of the failure of the auricular contractions.

Prognosis.—The gravity of stenosis of the tricuspid valve depends on its association with mitral stenosis in a great number of cases. Mackenzie supposes that tricuspid stenosis is a lesion which protects the rest of the heart from the ill effects of overfilling. This view is borne out by what was noticed in Gairdner's patient, who led the life of a laborer for many years without any symptoms that were obvious to the patient. When mitral stenosis is present at the same time, the additional lesion means a much greater strain on the cardiac mechanism, and the length of life in such case would be in proportion to the gravity of the lesion on the left side of the heart. In Newton Pitt's series of 87 cases, 31 died between twenty and thirty years of age, the others in a lessening proportion in the previous and succeeding age decades.

PULMONARY INSUFFICIENCY.

From the clinical standpoint so much that has been said about pulmonary regurgitation is either unproved or as yet incapable of proof that the subject should be approached with the greatest caution, and with as clear as possible a conception of the theoretical aspects.

Structurally the pulmonary valve and its surroundings differ from those of the aortic valve in their more delicate texture, and in the adult the segments do not, as a rule, show the medial thickening about the corpora Arantii. The wall of the pulmonary artery is thinner than that of the aorta and has not the same tendency to preserve its ring structure in the absence of an internal pressure. The conus arteriosus which leads into the pulmonary is more thin-walled than the corresponding part of the left ventricle, and under increased internal pressure is probably capable of considerable dilatation. The structures in relation to the pulmonary valve are obviously directed as a whole to withstanding much less pressure than the corresponding parts of the aorta, and this is borne out by what is known regarding the relative pressures in the two sides of the heart.

G. A. Gibson has shown that in the pulmonary artery of the sheep, pressures above 14½ inches caused a strong jet of water to escape through the pulmonary valve into the ventricle; with less than this, and down to a pressure of 9 inches of water, there was a small escape; below 9 inches the valves were competent. In the healthy human heart much fluid escaped with a pressure above 13 inches, a small amount between 13 and 8 inches, and none below that pressure. We have no direct means of estimating the pressure in man. The results of animal experiments give as the mean pressure 17.6 mm. of mercury in the cat, 12.07 mm. in the rabbit, and 29.6 mm. in the dog (Bentner). Eight inches of water is equal to about 15 mm. of mercury, so that the pressure in the pulmonary artery in man at the height of a vigorous systole of the right ventricle may cause a pressure well above that which first begins to cause insufficiency.

Etiology.—Insufficiency of the pulmonary valve may be caused by an acute endocarditis, by chronic fibrosis of the segments, or by dilatation of

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the orifice at the site of their attachment. Insufficiency from acute endocarditis is seen in gonorrhœa, rheumatic fever, pneumonia, scarlet fever, pyæmia, and puerperal fever. It is remarkable that in the cases collected by Newton Pitt from the records of Guy's Hospital nearly half those in which a definite infective cause was ascertained were due to the gonococcus. An interesting form is associated with aneurism of the aorta (Newton Pitt), in which an inflammatory change in the neighborhood extends to the pulmonary artery and causes an adhesion of one or more cusps of the pulmonary valve to it. Sclerosis of the leaflets is met with in long-standing cases of mitral disease, sometimes in emphysema and chronic affection of the lungs. Rupture and deficiency in the number of the valves are rare causes of insufficiency.

Relative pulmonary insufficiency may follow long-standing obstruction in the pulmonary circulation. Our knowledge of these conditions is very scanty, but those which are most certain are left-sided valvular disease, especially mitral stenosis (Graham Steell), and general pleuritic adhesions (Rokitansky).

Morbid Anatomy.—The endocardial changes associated with pulmonary regurgitation differ in no respect from those associated with other valves. In certain cases of infective endocarditis the orifice of the pulmonary artery may be narrowed by the vegetations. The right ventricle is enlarged to a degree depending on the duration of the insufficiency. The pulmonary artery may show patches of atheroma, especially if the insufficiency has been due to an obstruction in the pulmonary circulation, as, for instance, in mitral stenosis. It by no means follows that with evidence of pulmonary regurgitation during life this can be demonstrated postmortem; it depends wholly upon whether the elastic tissue of the base of the pulmonary aorta has been damaged. The ordinary methods of testing the efficiency of the valve postmortem, namely, by pouring water into the artery in the excised heart or measuring the diameter of the pulmonary orifice, only give the efficiency in the collapsed state of the organ, and not when it is distended by blood. This is probably the reason why in mitral stenosis it is often possible to detect a diastolic murmur down the left of the sternum and yet seldom is it possible to find evidence of regurgitation postmortem.

The other organs, in death from cardiac failure in this condition, differ in no respects from "cardiac" organs in other conditions.

Symptoms.—Only when failure of the right ventricle is present do symptoms appear, cyanosis, dyspnœa, œdema, failure of appetite etc. Epistaxis has been recorded in some of the cases, and in one case (Oliver's, 1907) it caused death. Hæmoptysis from emboli in the lungs is frequent in infective cases. A third group of cases are those in which the signs of an infective process, such as puerperal septicæmia, are the most noticeable, and, unless special attention be directed to the heart, are frequently not diagnosed during life.

Physical Signs.—The precordial area of pulsation is enlarged, the apex beat is to the left of the nipple line, diffuse epigastric pulsation is visible, and frequently pulsation to the left of the sternum in the second and third interspaces and jugular pulsation is present. The cardiac dulness is increased transversely. The auscultatory signs are the most important and those upon which alone a diagnosis can be made. The murmur of pulmonary regurgitation, as a rule, is coarser than that in aortic regurgitation, often grating, and

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more superficial. It is heard best down the left side of the sternum, and is propagated not along the systemic arteries, but along the left pulmonary artery. The second sound at the aortic area can usually be well heard, somewhat higher in pitch than that at the pulmonary valve, if present. It is often possible to detect pulsation in the lung vessels from the rhythmic constriction of the pulmonary alveoli; the vesicular murmur is rendered louder during ventricular systole.

Diagnosis.—In the case of pulmonary regurgitation, this is at all times difficult; the following points require special attention: (*a*) The character and situation of the murmur, its presence down the left side of the sternum and the rougher quality than that produced at the aortic valve. (*b*) The character of the pulse; Corrigan's pulse being invariably absent in pulmonary artery disease, though it should be remembered that Corrigan's pulse is not invariably present in aortic regurgitation. (*c*) The murmur of pulmonary regurgitation is increased in intensity during expiration or in expiration with a closed glottis (Valsalva's experiment). (*d*) The character of the apex beat, which in right-sided valvular disease is diffuse and displaced downward and outward.

Prognosis.—In the acute cases the outlook depends on the cause of the endocarditis. The streptococcus, gonococcus, and pneumococcus cases are usually fatal. In the more chronic forms some time is allowed for hypertrophy of the right ventricle, and not until this fails will there be signs of circulatory insufficiency. In relative insufficiency also a line of defence is present in the hypertrophy of the right ventricle; but the prognosis is associated rather with the original cause of the disease than with the pulmonary regurgitation.

PULMONARY STENOSIS.

This is an exceedingly rare acquired lesion. The congenital form is discussed in the section on congenital disease of the heart, and only the acquired form is considered here.

Etiology.—The causes are much the same as have been described in the section on aortic stenosis. (*a*) Endocarditis is the most common cause, and may occur in the course of rheumatic fever or one of the other acute infections. In some instances the vegetations are very large. (*b*) Chronic sclerotic changes may occur as at the aortic orifice, sometimes associated with endarteritis of the pulmonary artery. (*c*) Rare instances due to trauma have been recorded.

Morbid Anatomy.—The changes are much like those at the aortic orifice. In the form with endocarditis, the vegetations may be very large, and almost block the orifice. In some cases the process may be more in the conus arteriosus, and this is often due to endocarditis of the ventricular wall. In the sclerotic form the cusps are thickened, and may be adherent, forming a much narrowed orifice. Calcareous deposits may form, so that the orifice is nothing but a rigid ring, in which case the stenosis is accompanied by regurgitation.

Pathological Physiology.—Practically the same changes arise as are found in the left heart in aortic stenosis. With pure stenosis, hypertrophy of the right ventricle is the most marked early change, as by this compensation is maintained; but, when insufficiency is combined, dilatation and hyper-

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trophy result. With marked stenosis there must be some decrease in the pulmonary circulation. As the right ventricle fails tricuspid insufficiency will appear.

Symptoms.—As long as the lesion is well compensated, these will be few. There may be some shortness of breath on exertion, but this is usually not marked. The same may be said of œdema and the symptoms due to venous engorgement. With loss of compensation, dyspnœa and cyanosis may both be marked, and œdema of the legs and the symptoms of passive congestion appear.

Physical Signs.—On *inspection,* the apex beat may be somewhat out to the left, and there may be quite marked heaving pulsation over the lower sternum and adjoining left costal margin, as well as in the epigastrium. If there is loss of compensation, the veins in the neck are full, and show pulsation, as described under tricuspid insufficiency. On *palpation*, a systolic thrill is usually felt at the base, sometimes over rather a wide area, or especially marked in the second left interspace. On *percussion*, the area of dulness is increased to the right. The most important signs are obtained on *auscultation.* A systolic murmur is heard, usually with its maximum in the second left interspace close to the sternum. It is sometimes propagated upward and to the left. The murmur is generally very harsh, often extends throughout systole, and seems more superficial and closer to the ear than that of aortic stenosis. It may be heard over a considerable part of the chest, but is not transmitted to the vessels in the neck. In some instances the murmur has been described as being soft. The pulmonic second sound is usually absent, or very faintly heard. A diastolic murmur is present if there be pulmonic insufficiency. The pulse does not necessarily show any change until loss of compensation occurs, when it is small, weak, and sometimes irregular. Clubbing of the fingers is sometimes present.

Diagnosis.—In this the great rarity of the lesion must be kept in mind, and it should always be the last to be considered; every other possibility should be gone over before this lesion is diagnosed, and even then it is safe to still have doubts. The murmur of aortic stenosis may cause error, but the fact of the murmur of that lesion being transmitted to the vessels of the neck is important. The pulmonary second sound is usually present in aortic stenosis and absent in pulmonary stenosis. The character of the pulse may aid, that of aortic stenosis being suggestive. Certain congenital lesions may give difficulty, especially a patent ductus arteriosus, in which the murmur is often longer, and persists after the second sound.

Perhaps the most common error is to make the diagnosis on nothing but the presence of a systolic murmur in the pulmonic area. To keep in mind how frequently a systolic murmur is heard there without any valvular disease, is to lessen the chance of the error. Among these conditions of occurrence are (*a*) anæmia, (*b*) peculiarities in the relation of the lung to the heart, (*c*) in many healthy young individuals, especially after exertion, in whom its occurrence may be difficult of explanation. In all of these the murmur is usually variable and altered, especially by change in position and respiration. The other signs of organic disease are wanting. Occasionally the murmur of mitral insufficiency is heard high up on the left side of the sternum, and may give difficulty. The other signs, and especially the accentuated second pulmonic sound, are of aid in recognizing this.

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Prognosis.—This is grave, as a rule, although the rarity of the lesion does not allow of much deduction from experience. The condition of the right ventricle is most important. With any signs of its failing, the outlook is serious. One danger is the liability to pulmonary tuberculosis.

COMBINED VALVE LESIONS.

In nearly 50 per cent. of all cases the valve lesions are associated, either as a sequence, or two or more valves are affected at the same time. In the series of 1914 cases of valvular disease in the Edinburgh report, there were 230 with a double aortic lesion, 231 with a double mitral lesion, and 362 with various combinations of aortic and mitral lesions.

The same cause may act on two valves; thus, it is common in rheumatic fever in childhood to have the aortic and mitral segments attacked at the same time. Sclerosis may attack the aortic and mitral segments simultaneously. Occasionally an acute endocarditis involves the tricuspid as well as the aortic and mitral, and in a few rare instances all four valves are found affected. A common association is insufficiency of the mitral valves as a sequence of lesion of the aortic segments. This relative insufficiency occurs so soon as the dilatation of the ventricle reaches a certain grade. In long-standing cases the tricuspid valves also become insufficient, and this is also a common sequence of stenosis and insufficiency of the mitral valves. Insufficiency of the pulmonary valves may also be combined with chronic lesions of the mitral. In consequence of the heightened pressure behind the chronic mitral lesion, sclerosis of the tricuspid segments may follow with adhesion and gradual narrowing. The actual lesion of the valve is rarely pure stenosis or pure insufficiency. In the auriculo-ventricular orifices in particular, some degree of narrowing is usually present with the insufficiency. At the aortic orifices pure insufficiency of the arteriosclerotic type is comparatively frequent.

In connection with combined lesions one or two cardiac axioms are to be remembered. The rheumatic heart in children is very apt to have both valves on the left side involved. In adults, particularly in women, the lesion of the mitral is often single. In men aortic insufficiency may be the only lesion, to be followed as the heart enlarges by relative mitral insufficiency. Combined aortic stenosis and mitral insufficiency occur in a few cases of rheumatic endocarditis in young persons, and in later life is sometimes a consequence of chronic sclerotic changes.

As it is chiefly by the character of the murmurs that we estimate these combinations of valvular defect, it may be well here to speak of their indications. A diastolic murmur heard over the body of the heart with a direction of propagation down the sternum indicates insufficiency of the aortic segments. In a few rare instances insufficiency of the pulmonary valves is present. The murmurs produced during diastole at the auriculo-ventricular orifice have special characters and qualities. A pure systolic murmur heard anywhere over the body of the heart does not necessarily indicate a lesion of a valve. So numerous are the conditions under which it may occur that the single systolic bruit heard anywhere over the heart is of no moment as an indication of valve lesion. It must always be judged of in conjunction with other features. In any case the position of maximum intensity of the

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murmur, the direction of the transmission, the existence of hypertrophy of the heart, or of one special chamber, must be taken into consideration. Combined diastolic and systolic murmurs give a more definite indication of lesion of a valve. Heard at the base in an adult, we may be reasonably certain that the aortic segments are involved. Heard at the apex region, the indication of mitral valve lesion is not so definite. In a case of pure aortic insufficiency the systolic murmur at the base may be caused by slight roughening of the segments or of the intima of the aorta, while at the dilated mitral orifice there may be a loud systolic and a rough rumbling presystolic (Flint murmur), and both associated with relative insufficiency. In such a case a single valve lesion is responsible for four heart murmurs. In general, it may be said that the diagnosis of combined valve lesions from murmurs alone is not very satisfactory. Much more important data are to be had from the study of the state of the individual chambers and the knowledge of the general cardiac pathology. In a child with an enlarged heart and a double murmur at apex and base we are safe in diagnosing combined aortic and mitral valve lesion. In an adult man who has not had rheumatic fever a similar combination may be produced by aortic insufficiency alone. Both in women and men mitral stenosis alone, or with insufficiency, may be the only lesion; but in cases of very long standing the valves on the right side of the heart are almost certain to be involved. As a rule, the physician is in a safer position if he limits his diagnostic ambition to two valves. Clinically when lesions of three or four valves are determined with accuracy, mortifying postmortem disclosures are not unlikely to follow.

PROPHYLAXIS OF VALVE DISEASE.

That the profession as a whole scarcely appreciates the importance of preventive measures in disease of the heart is due in part to the fact that full knowledge is not yet available and in part to the difficulty in making efficient what we already have. There died of disease of the circulatory system in England and Wales in 1905, 2716 persons under fifteen years of age. If we exclude from this list the congenital cases, we may say that a large proportion of the remainder should come within the category of preventable disease. In four directions we may work toward the lessening of the incidence of heart disease: (1) In the all-important endocarditic group of the acute infections, rheumatic fever plays the important role, and we need a more careful investigation into the conditions under which this disease prevails. Two circumstances appear to favor it. The damp, unsanitary surroundings of the poor seem to be the factor in the chronic tonsillitis and pharyngitis to which so many children are subject. More and more the profession has come to the belief that the portal of entrance of the germs of rheumatic fever is the tonsils and adjacent pharyngeal tissues. Careful attention should be paid to the state of the nose and throat. A mouth-breathing child should be regarded always as an unhealthy child, and enlarged tonsils, and adenoids should be removed. Parents and school teachers should be aroused to the great importance of the throat and nose in the well-being of the child. Damp houses should be regarded as unsanitary. Wet cellars and wet walls favor the conditions under which rheumatic fever prevails. There is no single problem of greater impor-

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tance in preventive medicine than the reduction of the enormous waste of life in children in consequence of the rheumatic infection. (2) In a second group the cardiac breakdown follows overuse of the muscles. This is most often a myocardial affair, but in a considerable proportion of cases there is disease of the valve. In the large public schools, boys should be carefully examined before they are allowed to enter into running and rowing contests. In a growing heart, the developmental energies of which are taxed to the uttermost between the ages of fourteen and sixteen, it must be most hazardous to throw upon it the extra burden of providing a work hypertrophy. No matter how careful the training, no boy of fifteen runs a mile race without serious risk. Both in schools and colleges much more stringent supervision should be exercised by the authorities in the matter of athletics. In the occupations, heart disease has become less common. With the introduction of machinery and the use of the lift in the mines the liability to strain of the heart has lessened. (3) Syphilis, as a cause of heart and arterial disease, plays a very important role, and if we could ensure a more systematic and prolonged treatment of all cases, much would be done to lessen the liability to myocardial and valvular lesions, and especially to mesaortitis and aneurism. In the army and navy, more particularly, these preventive measures may be of service. Even in the community at large the proportion of individuals who have had syphilis is very large, and we all know the difficulty in ensuring proper treatment. (4) And lastly, all circumstances which lead to arteriosclerosis promote the sclerotic type of valve lesion. Hard work, alcohol, and overeating, particularly when combined with the high-pressure life, are very apt to lead to early degenerations.

Much may be done to promote the establishment of compensation and to postpone the final breakdown. In a rheumatic case with endocarditis it is to be remembered that it is not simply the vegetations, but the proliferative changes in the substance of the valve that have to be considered. The quiet life without strain and without special effort will enable a valve to heal with a minimum of damage. With the development of incompetency it may take months before the heart adjusts itself by hypertrophy to the new conditions. And the patient should be made clearly to understand the situation. It is always better to have a frank talk and explain the state of the "machine." Let it be expressed in mechanical terms, and make him understand that the difference between a healthy engine and his own is that in the former, for the ordinary purposes of life, only 25 per cent., say, of the horse-power is used, and there is a reserve of 75 per cent. to be called upon; whereas in his heart just the reverse conditions prevail, and while he may be perfectly comfortable using the 75 per cent. which he has to do for the ordinary duties of life, he has only a narrow margin of 25 per cent. for extra calls and emergencies. All circumstances that tend to depress the vitality and to lower the nutrition must be avoided, and he must be taught to adjust his life to his heart's capacity, or, in other words, to live within his cardiac income. For a young, energetic, muscular individual this is a hard lesson, and it becomes a serious problem how to adjust in proper measure exercise and diet in the varied conditions in life.

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TREATMENT OF CARDIAC INSUFFICIENCY.

During the establishment of compensation certain troublesome features are apt to arise which require treatment. It is not always easy to say just how far these depend upon the hypertrophy and dilatation themselves and how far upon associated neurotic states. Not infrequently we are consulted by young men or young women between the ages of fifteen and twenty who complain of uneasy sensations about the heart with throbbing and palpitation, sighing respiration, and sometimes shortness of breath on exertion. On examination signs of slight enlargement of the heart with overaction are present. This is really the well-known irritable heart of the young, or some speak of it as the developmental hypertrophy. Sometimes it would appear as if there was a disproportion between the growth of the heart and of the body. Overexertion, particularly in schoolboys and in young collegians, cigarette smoking, masturbation, and overuse of the bicycle are sometimes causes. The outlook in these cases is usually good. They should avoid overuse of the muscles, and tobacco should be interdicted. They should be moderate in diet, and the state of the heart should be carefully watched. It is not always well to make too much of the condition. Very often the unpleasant sensations of abnormal action are quickly relieved by lessening the diet, cutting off the more starchy articles of food and anything which causes flatulency. In other instances a few doses of spirits of camphor or aromatic spirits of ammonia may be needed, but, as a rule, all that is necessary is a careful regulation of the life.

Overcompensation is a condition not infrequently met with in the early stages of valvular lesions before the heart has, so to speak, "found itself." Unpleasant throbbing, with irregular action, feelings of fulness in the head, inability to rest comfortably in the recumbent posture, are among the important symptoms, or the patient may have severe nocturnal attacks of palpitation. Very often this is not so much due to anything in the heart itself as the associated nervous state or an impoverished condition of the blood. Rest in bed for a week with careful regulation of the diet may be enough; if the heart's action is very violent, an ice-bag may be placed over the precordia for half an hour at a time. There are cases in which this unpleasant feature persists and is a source of more or less constant annoyance.

The actual valve lesion of whatever nature is very little under the control of treatment. Prolonged rest and potassium iodide influence the acute proliferative valvulitis, but we cannot replace scar tissue nor can we dissolve calcified atheromatous plaques. The whole treatment revolves about the cardiac muscle, the establishment and maintenance of compensation, the relief of the symptoms of insufficiency or decompensation, and the treatment of certain special symptoms.

1. **The Establishment and Maintenance of Compensation.**—Given a free coronary circulation, even in a state of wretched nutrition, the heart will gradually accommodate itself to the most severe valvular lesion. The hypertrophy and dilatation are not only salutary, but without them the circulation could not be maintained. As a rule, the call for additional strength comes slowly, and, as already mentioned, it is the old story of the woman who carried a calf in her arms every day, so that when it was an ox

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she still could carry it. So in the slow onward progress of a valvular lesion, month by month, year by year, the daily strength becomes equal to the daily needs. One point at the onset comes up in nearly every case, Should the patient know of the existence of the disease? Most assuredly! It is impossible to carry out rational measures without his intelligent coöperation. The exceptions to this rule are very few. Occasionally a neurotic subject is upset and is frightened to perform the ordinary duties of life. One or two such instances have come under my observation, individuals who have had a perfect obsession about the heart lesion, a sort of pantophobia which has made of them wretched valetudinarians. In many cardiac conditions, however, it is neither necessary nor advantageous to tell the patient of the state of his heart. In the hypertrophy of arteriosclerosis or of chronic Bright's disease, or of a chronic pulmonary affection, no special benefit is derived from laying special stress on this feature of his case.

In the case of a young man the first thing to be considered is his calling. Very often it has been at a special examination for some service that the valve lesion has been detected. Under these circumstances he is excluded from a certain number of occupations, and he should, if possible, choose one in which the demands upon the muscles are not great. In the working-class this is, of course, a great difficulty; but, if possible, trades and occupations requiring much exposure and hard work with the muscles should be avoided. In the higher classes the professions with least strain, the clerical, the legal, and the occupations in which the work is sedentary, may be taken up. For persons with a little capital, who have not themselves to do the heavy work, gardening and small farming are very suitable.

To maintain compensation the diet should be simple, avoiding, in particular, excess of food. Often in the early stages the patients are anæmic and feeble, so that they require an abundance of good food, with plenty of milk and eggs, meat, and fresh vegetables. If there is a tendency to put on fat, the diet should be restricted in carbohydrates and the patient should not be allowed to take too much food. Beer and spirits are quite unnecessary. Moderate quantities of Bordeaux or Rhine wines may be allowed. In middle-aged men with aortic incompetency, if they have been accustomed to much spirits, a glass of whisky may be allowed at dinner. Tobacco may be used in moderation, but in young men it is best interdicted, so difficult is it to keep the use in moderation, and even two or three cigars or half a dozen cigarettes may cause irregularity. Tea and coffee may be taken in moderation, a single cup of coffee at breakfast and a cup of tea or coffee in the afternoon and another after dinner. No strict rule can be laid down about this, as even these small quantities may cause irregularity. The question of exercise is always the most important in connection with valvular disease, and it is not at all easy to reach a happy medium. It should be understood that in a great majority of well-compensated lesions moderate exercise is of advantage. Regular systematic exercise, as in walking, easy cycling, horseback exercise, and golf, may be taken. For young men the more violent sports, such as football and hockey, should be interdicted. Golf is a particularly suitable game for young men, indeed, for men of all ages with well-compensated lesions. They should be warned, however, not to overdo it and not to play to the limit of tire, and the test of damage is the occurrence of dyspnœa or exhaustion. When outdoor exercise cannot be taken, systematic gymnastic movements may be employed. One is constantly

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asked, in the case of young girls, about dancing. With a simple mitral lesion perfectly well compensated and the apex beat not very far out, it may be allowed in moderation. Each case must be decided by itself. There are many instances in which it has not been at all hurtful. Hill-climbing and walking in the Alps may be very beneficial if not pushed to an extreme. After all, the test of any exercise is the result. If the patient is helped by it, if he is not made short of breath when at rest, or if it does not cause attacks of palpitation or nocturnal dyspnœa, it may be continued. As a rule, patients with valvular lesions should not go to very high altitudes. This is a good rule, to which, however, there are many exceptions. In a well-compensated mitral lesion there may be no difficulty. On the other hand, the patient may feel a good deal of distress at any altitude above 6000 feet.

Special care should be taken of the bowels, and if there is any tendency to corpulency an occasional saline purge may be used. The skin should be kept active by a daily bath. A cold tub in the morning may be taken if there is a good reaction afterward; if not, a lukewarm bath at night. Very hot baths should be avoided. Young people should be allowed plenty of sleep, and in the early stages of well-established compensation an hour's rest in the middle of the day is helpful. It is impossible to lay down hard-and-fast rules to meet every case, but the physician should try to reach the happy medium between overanxiety and unnecessary precaution, and allowing the patient a liberty which may lead to early decompensation. "Moderation in all things" should be the motto of the patient.

Two or three special points may be referred to. The question of marriage is always a distressing one, particularly if before the onset of the lesion the patient's affections have been engaged. Everything depends upon the lesion and the stability of the compensation. In young women with simple mitral incompetency there seems to be a minimum of risk. In many such cases they become the mothers of large families without the slightest damage to the heart lesion. It is to be remembered that often a lesion reaches a stationary point and the heart is really a first-class piece of mechanism, with only 50 per cent. less reserve than in a normal one. Always in this connection the writer calls to mind a patient who has been under his observation for many years, in whom a mitral insufficiency followed rheumatic fever at sixteen. With a loud apex systolic murmur, and signs of moderate enlargement of the left ventricle, this woman has had nine children and has lived to be more than sixty years of age. The extreme mitral stenosis is not so favorable, and yet in how many instances has one seen repeated pregnancies safely carried through with quite advanced stenosis. Combined mitral and aortic disease with great enlargement of the heart and tumultuous heaving of the chest wall and slight protrusion should interdict marriage. The middle-aged Lothario who is shocked to find (perhaps as the result of a life insurance examination) before the contemplated marriage that he has an aortic insufficiency should be warned of the dangers. But these are cases in which, if the physician is wise, he will simply express an opinion on general grounds, as his specific advice is almost certain not to be taken.

In young persons special pains should be taken to prevent intercurrent diseases. In children the condition of the throat should be watched with the greatest care, and if there is the slightest enlargement of the tonsils it would be better to have them thoroughly removed. The state of the mouth should be carefully watched, bad teeth removed, and a visit to the dentist

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should be paid once in three months. When possible, for a year or two after the establishment of compensation the patient should be carefully watched, and during the winter months a change of climate is most helpful—to Florida, Southern California, the South of France, Italy, Egypt, or Algiers.

2. **Treatment of Loss of Cardiac Compensation.**—At any stage in a valvular lesion or in hypertrophy and dilatation of the heart from any cause, *acute cardiac insufficiency* may arise, associated with dyspnœa, more or less cyanosis, irregular action of the heart, the gallop rhythm or embryocardia and a small rapid pulse. In typical form this is seen in the cases of arteriosclerosis, in hypertrophy and dilatation from overexertion, but it may occur in any form of valve lesion. It is the one condition in heart disease in which a venesection is advantageous. For many years now this practice has been carried out at the Johns Hopkins Hospital with the greatest benefit. In many hands it is not satisfactory, because sufficient blood is not taken. Good results are rarely seen unless as much as twenty ounces is taken. To "breathe a vein" skilfully is now almost a lost art, and to get enough blood it is sometimes necessary to bleed from both arms. Hypodermics of ether in dram doses, strychnine hypodermically in $\frac{1}{30}$ or $\frac{1}{20}$ grain (0.002 to 0.003 gm.), or digitalin, $\frac{1}{20}$ to $\frac{1}{12}$ grain (0.003 to 0.005 gm.), may also be given. Camphor, either by the mouth (the tincture in dram doses) or hypodermically, in doses of 2 grains (0.13 gm.) dissolved in olive oil, is useful. Local applications to the heart may be tried, a hot-water bag as hot as can be borne or a mustard leaf. If the case seems desperate, cardiocentesis may be practised. The needle is thrust boldly into the heart substance in the fourth or fifth interspace. Reading the successful case reported by Sloan some years ago, one cannot but feel that this measure, desperate though it seems, may occasionally be useful. The senior author has only practised it twice himself, in neither instance with any special benefit.

In a majority of instances the failure in compensation is gradual, and it takes a week or two before the signs are well established. The first and all-essential requisite is:

Rest of the body may, indeed, be the only thing necessary. Time and again, to demonstrate its importance to students, the senior author has treated patients with this measure alone, combined, perhaps, with a brisk saline purge, and within a few days the œdema of the feet disappears, the bases of the lungs become clear, and the heart's action quiet and strengthened. In many instances the chief value of a consultation has been in the insisting upon absolute rest. It is not always possible to induce a patient to go to bed, nor is it always possible for him to remain in bed. In the milder grades of cardiac breakdown the semirecumbent posture may be maintained, but it too often happens that the condition is one of orthopnœa, and there is no possible position of comfort in bed. The patient then has usually to sit up out of bed, and he is fortunate if there is available an old-fashioned "grandfather's chair" with the comfortable side pieces for the head. One of the greatest difficulties in the nursing of these cases is to get a position in which the patient may sleep comfortably. Too often, just as he drops off, the head falls and he wakens with a start. An ingenious nurse may sometimes be able to devise methods for the support of the head, but it is by no means easy. Sometimes these patients get into all sorts of remarkable attitudes. One poor fellow with a cardiac breakdown following emphysema had comfort only in the knee-elbow position. Patients may be able to sleep kneeling

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at the side of the bed. One man for weeks could get relief only by leaning forward on to the back of a chair against which he rested his forehead, on which, in spite of every precaution, he had a bedsore. The greatest care should be taken of the back, but nowadays, with modern nursing, one rarely sees the terrible bedsores which were common thirty or forty years ago. Sooner or later there comes a stage when there is more or less permanent cardiac insufficiency which neither rest nor medicinal measures is able to overcome. The patient is tired of bed, and under these circumstances it is often beneficial to let him be up and about for part of the day, even if the exercise does bring on shortness of breath and increase the irregularity of the heart. In these chronic cases, when possible, the bed should be wheeled out-of-doors, or they may sit up on the couch on the veranda for part of each day, or be taken out in a wheeled chair. The question of systematic exercise will be considered in connection with the special methods of treatment.

Diet in the treatment of cardiac insufficiency is one of the most important and at the same time difficult elements in the treatment. We have all been notorious sinners in overfeeding our heart patients, particularly in the stage of broken compensation. The stomach is not only a near but a bad neighbor to the heart. With venous stasis of the gastric mucosa it is impossible to have a good gastric juice, and it is a good rule for the first few days, when the patient comes under treatment, to give a minimum quantity of food until with saline purges the overloaded viscera are relieved. A patient will get along perfectly well with the whites of six to ten eggs, flavored with lemon; this is very palatable, and in three or four of the feedings a little whisky or brandy may be given. Freshly prepared beef juice, milk diluted with lime-water or soda-water, and whey are also suitable. Not too much should be given, and when there is nausea or vomiting it will do no harm to let the patient go for twelve hours without any food in the stomach, and at intervals very hot water may be given, and if it be thought necessary, rectal enemas may be used. All prepared starchy foods are, as a rule, contra-indicated. Patients differ very much in their tastes and gastric capacities, and to a certain extent these may be humored. As soon as possible the patient should be taken off the "slops" and given solid food in small amounts; care should always be taken not to fill the stomach too much with liquids and solids at the same time. The sensible doctor will not forget that even a perfectly healthy stomach could not stand the heroic medication which we sometimes encounter, three mixtures—necessitating a dose at least every two hours, often a nocturnal pill, the nocturnal purge, the morning saline and sleeping draught at night! Too often this Arabian polypharmacy defeats the very object we have in view.

Reduction of Intake of Liquids.—It is by no means easy to decide just in what class of cases liquids should be restricted. Theoretically, the ingestion of large quantities of fluid increases greatly the work of the heart, and we know hypertrophy is caused directly by this in beer drinkers. On the other hand, there are many conditions in which it seems necessary in order to promote diuresis and sweating to give large quantities of fluids, milk, barley-water, and fluids generally. The following may be taken as indications, but they must be modified to suit the conditions. When compensation is good the patient should be careful not to take too much liquid, but the quantity of urine should not be allowed to fall below a normal limit. Such patients should not be allowed to take "cures" indiscriminately, as the drink-

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ing of very large amounts of liquid may lead to pronounced embarrassment of the heart. In very stout patients with valvular or myocardial lesions the meals should be taken as dry as possible, and fixed quantities of liquid given during the day, enough to keep up the output of urine. The cases which demand reduction of the liquids are those with cardiac dilatation and venous stasis and œdema. Combined with purgatives the reduction in the total of the liquids to one and a half pints given at stated intervals, either milk and soda-water or milk and barley-water or albumin-water, may have a very beneficial effect on the dropsy and promotes the flow of urine; under these circumstances, too, the digitalis acts more favorably, as well as other remedies, such as diuretin.

Special Methods.—Certain plans of treatment have been introduced—combinations of diet, exercises, and baths.

Oertel's Method.—The late Professor Oertel, of Munich, who had a vast experience with the heart lesions of stout beer-drinking Germans, devised a method of treatment which is often most satisfactory in the weakened heart of obese persons. He sought to reduce the quantity of blood, to increase its concentration, and to diminish the amount of fat. The treatment consists in, first, the reduction in the amount of liquid. A total of about 36 ounces is allowed in the twenty-four hours, which includes the amount taken with the solid food. Baths and sweating help still further to reduce the quantity of water in the body. Secondly, the diet, which is chiefly proteid:

Morning.—Cup of coffee or tea, with a little milk, about 6 ounces altogether. Bread, 3 ounces.

Noon.—Three to 4 ounces of soup; 7 to 8 ounces of roast beef, veal, game, or poultry; salad or a light vegetable; a little fish; 1 ounce of bread or farinaceous pudding; 3 to 6 ounces of fruit for dessert. No liquids at this meal, as a rule, but in hot weather 6 ounces of light wine may be taken.

Afternoon.—Six ounces of coffee or tea, with as much water. As an indulgence an ounce of bread.

Evening.—One or 2 soft-boiled eggs; 1 ounce of bread; perhaps a small slice of cheese, salad, and fruit; 6 to 8 ounces of wine with 4 or 5 ounces of water. The third and most important are exercises, the so-called "*Terrain-cur.*" Graduated walking exercises are taken, not on the level, but uphill at various grades. A definite amount is done each day and the distance is gradually increased. Undoubtedly, at proper resorts suitable cases are greatly benefited by this plan of treatment, but it is to be borne in mind that Oertel recommended it particularly for the stout individuals with weakened heart action.

Nauheim Method.—Here the great influence is believed to be affected through the stimulating influence upon the heart of hot CO_2 saline baths combined with special muscular exercises. The precise mode of action is still under discussion, some attributing the good results to the stimulating influence of the CO_2 on the nerves of the skin; others regard the temperature of the bath as the most important element. Whatever the precise *modus operandi*, the heart is stimulated to more vigorous contraction and the area of heart dulness is diminished under observation. It has been suggested that this may be only the effect of Abraham's cardiac reflex. By reducing the temperature of the bath and increasing the concentration of the salts the heart's action is still further stimulated, and it becomes progressively

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strengthened. Schott gives the following directions for the artificial baths and for their general management "Commercial bicarbonate of sodium and crude hydrochloride acid (42 per cent.) are added in equal quantities by weight to the bath water. This leaves a slight excess of the alkali, which is useful for protecting the metal bathtub and at the same time the patient's skin.

"In the beginning 100 grams of each should be added to a bath of about 250 liters of water, and this quantity may be gradually increased until 1500 grams of each ingredient are added (250 liters or quarts are equal to about 62 gallons; 100 grams are equal to about $\frac{1}{5}$ of a pound; 1500 grams, about 3 pounds). The bicarbonate of soda is first dissolved and poured into the bath water, while the hydrochloric acid is not added until everything else is ready. The acid should be poured out under the water, holding the mouth of the bottle over the bottom of the tub and gently moving it about in all directions as the acid escapes. When the bath is to be prepared in a hurry, the mouth of the bottle is held immediately below the level of the water and moved rapidly to and fro without splashing. The layer of carbon dioxide which forms above the surface of the water must be removed by fanning, the window being open. The maximum duration of the bath is twenty minutes.

"At the beginning of the treatment most patients require an occasional day of rest, on which the bath is omitted, sometimes after the first, but usually not until after the second bath. After that the number of baths given in succession without an interval of rest can soon be increased.

"As a matter of precaution the bath should always be omitted on one day of the week.

"The patient's general condition and the condition of the heart must be kept constantly under accurate supervision; the effect of the bath determines the temperature and duration of the next one." Schott lays great stress on the subjective sensations of patients who are receiving the bath treatment: "If a patient feels tired for one or two hours after the first bath and then recovers completely, he may be given the same bath on the following day; but on no account may the strength of the bath or its duration be increased. If the fatigue lasts longer than two hours, the bath should be omitted on the following day. This principle should be observed during the entire course of treatment. When a series of baths of increasing strengths have been prescribed, each bath must be regarded as a task which the patient must be able to accomplish without any subsequent fatigue before he is allowed to take up the next. If he does become unduly fatigued, the course is begun over again after a day's rest with a bath of slightly diminished strength.

"The strength of the bath should be increased as rapidly as possible until a distinct effect is obtained, carefully avoiding any excess. Unless the invigorating effect on the heart is noted immediately after the bath during the beginning of the treatment, the bath is not sufficiently strong. The pulse ought to become slower and stronger, and a distinct reduction in the size of the cardiac dulness ought to be demonstrated immediately after the bath. This reduction in the size of the dulness should always be the object aimed at, even if it does not persist the entire day." Resistance exercises are given by a trained attendant, and definite groups of muscles are systematically brought into action.

Nauheim has become a vogue, and all sorts and conditions of patients

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from all parts of the world flock there, so that it is by no means easy to form an unbiased judgment on the value of the method. The senior author has been watching carefully the results in many patients who have been under treatment there. They may be divided into three groups: Scores of persons who have nothing whatever the matter with their hearts are greatly benefited by the change and the holiday. In a second large group much damage is done. For years the senior author has been in the habit of seeing victims of the Nauheim cure, many of them physicians, who have come for advice regarding the long train of troublesome symptoms of the neurotic heart. Frightened by a little irregularity, they have submitted themselves to a Nauheim "cure," and have been greatly alarmed to find that instead of improvement they have grown worse. In many neurotic women the last state has been much worse than the first. As a rule, these patients are little if at all benefited. Cases of aneurism, valvular disease in the late stages of broken compensation, arteriosclerosis with very high pressure, do not seem to have done well under this special method.

A third group, in which good results are seen, comprises the chronic myocardial cases, the fat patients with weak hearts, the cases of valvular disease with slight disturbances of compensation, but not with dropsy. The baths may be carried out at home, but the same beneficial results are rarely obtained, even in suitable cases. As so often happens in these special forms of treatment an opportunity is given for unscrupulous practitioners to impose upon patients, and the Nauheim method has not always been carried out with common-sense. A plentiful lack of judgment has characterized the treatment of many individual cases that have come under observation. One thing should be demanded of those who carry out the treatment at Nauheim or elsewhere: they should stop alarming people who have little or nothing the matter with their hearts.

Medicines which Strengthen the Heart's Action and Help to Restore Compensation.—Among these digitalis not only takes the first rank, but is in a class apart. Introduced in 1785 by William Withering,[1] one of the most distinguished of English physicians and botanists of the eighteenth century, it divides with quinine the honors of the galenical pharmacopœia. Withering's work is one of the most memorable contributions ever made to therapeutics, and the inferences which he draws from a series of 163 cases of his own and a number from his correspondents hold good today. The various forms of dropsy were, of course, not distinguished at that time, but he recognized that the most hopeful for treatment with digitalis were those with a feeble and intermitting pulse.

Evidence has been accumulating to show with much greater accuracy the effect of digitalis on the various functions of the heart.[2] *Excitability* is not a function which is affected to the same degree as the others, yet the frequent presence of *pulsus bigeminus* is evidence of a hyperexcitability of the ventricle and the production of an extrasystole in the more rhythmic parts of the ventricle. The second beat in pulsus bigeminus is never preceded by an auricular beat. On the other hand, when the heart has a disorderly rhythm,

[1] An account of the Foxglove, etc., Birmingham, 1785.

[2] For further reference, the reader is referred to Cushny's text-book and the following papers: Wenckebach, *Die Arhythmie des Herzens*, Leipsic, 1903; Mackenzie, New Methods of Studying Affections of the Heart, *British Medical Journal*, 1905, vol. i; Gibson, *Quarterly Journal of Medicine*, Oxford, i. 173.

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such as occurs in mitral stenosis (a condition probably due to overstretching of the auricle and an inception of the heart rhythm by the ventricle), then digitalis may have the effect of allowing the auricle again to dominate the rhythm, which then becomes regular, not so much perhaps from a depression of ventricular excitability as from a diminution of the auricular dilatation and lessened interference with those parts of the auricle which normally start the beat.

The effect of digitalis on *contractility* is one of the greatest dangers of its action. The action of digitalis in producing a pulse of just half the rate of the ventricle is well known. This is due to a depression of the function of contractility, and gives rise during the earlier stages to the condition known as *pulsus alternans*. If its action is allowed to continue, it produces half the rate of beat in the arteries, the second beat being unable from its feebleness to produce a wave in the arteries. Later the second beat may be entirely suppressed even at the heart. Wenckebach's explanation is that the normal depression of contractility which follows each beat is much greater under the action of digitalis, and that when the second stimulus from the auricle reaches the ventricle the latter is only able to respond in a feeble manner.

Conductivity is a function which has been shown by Mackenzie to be markedly depressed by digitalis. When such an effect is present it takes the form of lengthening the interval, normally about one-fifth of a second, between the beginnings of the auricular and ventricular impulses. It produces exactly the same effect as gradual mechanical compression of the auriculo-ventricular bundle in the dog (Erlanger), and results in a dropping out of certain ventricular contractions; hence this is another way in which digitalis can produce an abnormally slow pulse. But in some cases digitalis does not produce an effect on conductivity, unless given in enormous doses, which points to involvement of other factors. Of the effect of digitalis on *tonicity*, there is the invariable clinical observation that it is of the greatest use when dilatation is present, and the benefit which comes from it is due to a stimulation of this special function of the heart muscle. It may be taken as a guiding rule that digitalis will not do any good unless dilatation is present. The early slowing of the heart when digitalis is administered is due to its effect on *rhythmicity*. The longer diastole allows of a much greater restitution of the other functions, especially that of contractility, and the whole cardiac mechanism is benefited.

Digitalis is indicated when the heart's action is weakened to the degree of insufficiency. Neither feebleness of action nor irregularity are in themselves indications. Not until the effects of such weakness become manifest in shortness of breath, cyanosis, or œdema is the drug indicated. As a rule, the type of valvular lesion makes no difference whatever, as the cardiac insufficiency, for which the digitalis is almost a specific, is an affair of the muscle, not of the valves. In the common triple combination characteristic of insufficiency—dyspnœa, venous stasis, and dropsy—experience has fully borne out the ninth inference of Withering, "that digitalis has a power over the motion of the heart to a degree yet unobserved in any other medicine."

In cases of acute cardiac insufficiency the good effects are not so striking, and patients admitted in a state of cyanosis and orthopnœa and embryocardia are much more promptly relieved by copious venesection. The results of the administration of the drug are often phenomenal. The patient, who has been in a desperate state, may within a few days be rendered com-

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fortable.[1] Relief of the thoracic oppression and of the dyspnœa, lessening of the cyanosis, and increase in the flow of urine are the indications of beneficial action.

The contra-indications for the use of digitalis are much more numerous than the indications. Few valuable drugs are so much wasted. Neither rapidity of action nor arhythmia are in themselves indications, unless accompanied by signs of weakness of the muscles. There are many cardiac irregularities over which digitalis has no control, and persistency of irregularity is neither a contra-indication nor an indication for its use. In many cases the signs of heart failure in mitral disease disappear under its use, while the irregularity persists. It may be said broadly to be contra-indicated in all forms of heart disease without symptoms of muscle weakness; it is contra-indicated, too, in the great majority of cases in which the patients come complaining of their heart, of irregular and violent action. Such cases are much more satisfactorily treated by attention to their digestion and the nervous condition. In states of high arterial tension digitalis is contra-indicated. One is sometimes placed in a quandary, as the paradoxical features may be presented of a dilated heart with gallop rhythm and blood pressure considerably above the normal. Under these circumstances the latter may be discounted. But in middle-aged men with permanent high tension, sclerotic vessels, and a hypertrophied left ventricle, digitalis may be directly hurtful. In angina pectoris, as a rule, the underlying conditions are not those which are modified by digitalis. In a few cases where the heart's action is feeble, gallop rhythm is present, and particularly where the angina is directly associated with a very old valve lesion, more particularly in mitral cases, digitalis may be used without risk. In aneurism the drug is not of any service, except in the rare cases when the dyspnœa and œdema are directly due to heart weakness. There is widespread belief in the profession that digitalis is contra-indicated in insufficiency of the aortic valves. In the periods of decompensation the drug more frequently fails than in corresponding mitral cases, and we more frequently see death in heart cases in aortic insufficiency during the administration of digitalis; but this is particularly in the arteriosclerotic group when the nutrition of the heart muscle is failing, and when, as so often happens, the coronary arteries are seriously involved. In a majority of instances just as good results are seen in this lesion as in mitral cases, but a little more care has to be exercised in its use.

With the common gastric disturbances of broken compensation, digitalis, as a rule, is not well borne, as it often aggravates nausea and vomiting. Under these circumstances it is much better given hypodermically as digitalin. Toxic symptoms, which are not very often met with, follow the employment of very large doses or, occasionally, the prolonged use. Nausea, vomiting, sometimes diarrhœa, with pallor of the face, feeble, rapid pulse, and dimunition of the amount of urine are the special features. There are three useful indications when the patient has had enough digitalis. The pulse becomes slow, but it must be remembered that one of the characteristic actions of the drug is the production of the bigeminal pulse. The second beat may

[1] For the young physician there is no other reputation-producing medicine of the same rank with digitalis, and it is one of the dozen drugs the uses of which repay a lifelong study. How he uses it may be taken as a sort of indication of the therapeutic intelligence of the practitioner.

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become feebler, and finally is not perceptible to the finger. It may at the same time be evident as a small beat in the tracing, and the corresponding sound may be heard at the apex. The pulse may be counted at 40 when the heart beats are 80, or at 60 when they are 120. Mackenzie, Hewlett, and others have studied this peculiar action of digitalis, which may produce a definite type of heart-block. Hewlett has reported cases which seem to show that the combination of atropine prevents this effect. The condition is common in mitral cases, and may keep up for weeks without any special risk, but it may be followed by a rapid feeble action of the heart. The second important indication is a lessening of the flow of urine. Directions should always be given to measure and record the daily quantity, as a reduction gives one of the earliest indications when the useful action of the drug on the heart and vessels has ceased; and thirdly, a progressive lowering of the blood pressure is, as a rule, an indication to stop the drug.

Mode of Administration.—The judicious practitioner will study the use of three or four preparations which have stood the test of many years and will look askance at many of the new-fangled preparations of the drug. There are four preparations which he may use with advantage.

The Tincture.—In a patient with mitral or aortic lesion, who has just begun to have shortness of breath with swelling of the feet and diminution of the amount of urine, a good plan is to give the tincture in 15 minim doses every four hours for two days. Then it may be stopped for twenty-four hours and resumed for another two or three days, and so continued at intervals. Usually within ten days or two weeks the serious symptoms have disappeared and the drug may be stopped, or continued in 5 minim doses three times a day. As a rule, the tincture answers admirably, unless the stomach is very irritable.

The *infusion* in half-ounce doses, four to six times a day, is equally efficacious, and is believed by some to be more diuretic in its action. When the stomach is irritable it is not so well borne.

Powdered digitalis is of great service, in combination with squills and mercury, a grain of each in the form of the Addison or Guy's pill. It is particularly indicated in the cardiac failure of old arteriosclerotic patients, those with chronic nephritis, and more particularly when there is swelling of the liver, ascites, and jaundice.

The so-called active principles of the digitalis, digitalin and digitoxin, have been much used. The only advantage of digitalin is that it may be given hypodermically when the stomach is irritable. To get any good effects from the ordinary digitalin (Merck) it must be given in large doses, $\frac{1}{30}$ to $\frac{1}{20}$ or even $\frac{1}{12}$ grain (0.002 to 0.003 to 0.005 gm.) every four hours, watching its effects carefully.

For how long may digitalis be used without danger? There is not much risk of cumulative action with sudden untoward manifestations. As a rule, the symptoms above referred to suggest at once that the patient has had enough. Twice the senior author has known the digitalis habit to be contracted, in which over a long period of years patients took the tincture, in one case 5 and in the other 10 minims two and even three times a day. One was a physician with aortic insufficiency, who had taken digitalis daily for more than twenty years. He had a fixed idea that without it his heart became feeble. The remarkable thing was that he never had unpleasant effects.

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Substitutes for Digitalis.—There are none, but it occasionally fails and there are other remedies which have an action on the heart of the same character, but less constant and enduring. Among those strophanthus takes the first place. It may be used in the form of the tincture, of which 10 minims (0.6 cc.) may be given every three or four hours. Its constricting effect upon the smaller arteries is said to be less than digitalis. It is very often useful to keep up the action of the heart after a course of digitalis, and in children with old mitral lesions it is sometimes better borne. As a rule, it is rarely found to be efficacious when digitalis fails. Sparteine, in 1 grain doses of the sulphate, adonis vernalis, and convallaria may be sometimes useful. Camphor is much used by the Germans; caffeine and theobromine are also recommended, but in failure of the heart muscle they are not of much value in comparison with the preparations of digitalis. Strychnine by mouth or hypodermically in acute conditions is often of service, and may be given with the other remedies. Depending on the condition, it may be given in doses of $\frac{1}{60}$ to $\frac{1}{20}$ grain (0.001 to 0.003 gm.).

3. **Treatment of Special Symptoms.**—Cardiac dropsy is usually relieved by the digitalis. When resistant, it forms one of the most difficult symptoms to overcome. The use of the saline laxative, particularly the salts given by May's method in concentrated form early in the morning, the compound jalap powder, or calomel purges, are very helpful. To promote sweating, hot baths, either the very hot tub, the steam bath, or the hot-air bath, may be tried cautiously. On the whole, it may be said that this is not so satisfactory in cardiac as in renal dropsy, and it is sometimes very difficult to get a profuse action of the skin. The hydrothorax and the ascites may require tapping. If the anasarca of the legs becomes very great, the skin may be punctured either with the small Southey's trocar, or small incisions may be made in several places on the legs. Dressed with gauze and thick layers of sterilized cotton, an enormous amount of fluid may be drained away. It is, as a rule, perfectly safe when the usual precautions to avoid infection are taken. In milder grades of the anasarca it is very helpful to bandage the legs firmly.

Sleeplessness and Restlessness.—With failure of compensation the patient has almost always bad nights, and the question of the use of hypnotics comes up at an early date. It is well at first to try the milder forms. Paraldehyde is often very satisfactory, given in dram doses; the patients become accustomed to the unpleasant odor. Veronal or trional alone or combined with potassium bromide may be tried. When the milder hypnotics fail, as they often do, opium should be used. While it is contra-indicated with a low output of urine and the presence of a great deal of bronchial catarrh, it is perhaps next to digitalis the most favorable drug in the treatment of the heart itself. In the cardiac failure of arteriosclerosis, with the terrible nights of orthopnœa and restlessness, hypodermics of morphia give the greatest relief. We are, altogether too cautious in the use of this drug, which is of incalculable service in the severer manifestations of the disease. Given in small doses of $\frac{1}{8}$ grain (0.008 gm.) hypodermically it may be repeated in a few hours if rest is not obtained. In children paregoric is very helpful, and it may also be used in the attacks of nocturnal palpation in the irritable heart.

Anæmia.—This should always be kept in mind, and if present, iron and arsenic should be given as soon as the acute cardiac features are over. Some patients are greatly helped by occasional courses of these drugs.

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CHAPTER VIII.

FUNCTIONAL DISEASES OF THE HEART.

By CHARLES F. HOOVER, M.D.

The prognostic distinction between anatomical and functional disease of the heart is not so sharply drawn as in former years. Anatomical diseases of the heart were formerly the only cardiac affections which were linked with grave prognostic significance. Functional disturbances of the cardiovascular system were in former years not associated in the minds of medical men with heart death. Our present conception of functional disease of the heart is not at all inconsistent with the ultimate death of the heart. Even in heart death following organic disease we are now becoming more accustomed to the conception of functional death of the heart, separate from the idea of an exhausted muscle struggling against great odds.

Attention has been directed to the failure of diastole, in contrast to the failure of systole, at death of the heart, so that this idea of heart death from disorder in the nervous impulses to the heart enters more and more into our conception of the natural history of heart diseases. Anatomical diseases of the heart may precede a functional disturbance, but, on the other hand, a functional disease of the heart may terminate in an anatomical disease. We know the persons most frequently affected by diseases of the heart muscle and vascular system are those who in early life have suffered from neurasthenia or hysteria, or by their mode of life have subjected the neurovascular system to oft-repeated insults, which, although apparently mild in their single events, have produced, collectively, final histological changes in the myocardium and aortic system. It is a common practice of physicians to console patients with the remark, "The heart is of normal size and the sounds are clear." Many of the laity have learned that such an assurance offers little consolation. We see some instances of myocardial incompetence following prolonged intense mental and emotional distress. One instance was in a woman, aged forty years, who had experienced great mental suffering on account of domestic infelicity. She had exhibited many stigmata of hysteria during the period of ten years before she came under observation. She had dilatation of both the left and right ventricles with cardiac arhythmia. There was not the slightest sign of any disease of the kidneys, heart valves, the aorta or its branches. The distribution of the blood was perfectly normal, in marked contrast to the laboring heart. There was nothing in the history of the preceding ten years on which one could base the suspicion of former venous stasis in the lungs or systemic venous system. This patient died two years later directly after the death of her only child. Unfortunately no autopsy was obtained, so the character of the myocardium could not be learned. This patient appeared to be an instance of the so-called "broken heart." In another patient with a rapid, irregular, and slightly dilated heart, there was nothing further in the physical status to account for the myocardial

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disturbance. On inquiry it was learned that the social condition of the patient was extremely bad; she had been suddenly reduced to want and had lost several members of the family by death. A few months later the woman appeared with a perfectly rhythmic heart and normal percussion lines. The social distress of the patient was relieved in the meantime, and with this relief the cardiac distress disappeared.

Many damage suits in our courts involve the question of whether the patient's heart affection is due to a lesion or merely functional disturbances which have resulted from mental shock. These evidences of cardiac disturbance are frequently very difficult to classify. All of these instances of cardiovascular disturbances which come under the head of traumatic neuroses and those which follow upon prolonged and severe mental distress must be regarded as the direct result of an unfavorable influence on the cardiac innervation through the cerebral cortex; but we shall see later there are many symptoms in the circulation which result from unfavorable influences on the cardiac nerve centres from impulses in remote nerve distribution—for example, the cardiac neuroses which accompany disorders of the abdominal and pelvic viscera. Our knowledge of nerve paths involved in cardiac innervation compels us to regard both classes of disease as reflex in character. Both of these classes of reflex cardiac disease may eventuate in anatomical lesions and in heart death. If we consider for a moment the very severe treatment applied to nerve paths in animal experiment before we can elicit tachycardia, bradycardia, and cardiac arhythmia, the very symptoms which we commonly see as a result of severe mental distress, prolonged emotional excitement, or disease of the gastro-intestinal tract or pelvic viscera, we may have some conception of the severity of nerve impulses in these every-day affections which we are apt to treat too lightly in nervous patients. Furthermore we find very decided anatomical lesions in the heart and aorta secondary to organic diseases of the central nervous system.

Tessier[1] reported a case of locomotor ataxia in which the segments of the aortic valve were very much thinned. There were also seven perforations of one segment of a valve in a space of seven millimeters and the aortic wall was sound. Friedreich reported a case of hereditary ataxia in which the segments of the aortic valve were so thin that he compared them to rice-paper moistened with water. Tessier also reports a case of beginning locomotor ataxia in which rupture of the aortic valve occurred after an all-night march in the cold. The same author reports another case which has an interesting significance relative to trophic and functional disturbances in the heart attending diseases of the nervous system and traumatic neuroses. This patient had traumatic cervical spondylo-arthritis attended with dilatation of the right heart, arhythmia, and a loud systolic murmur; all of which disappeared after recovery from the symptoms in the cervical vertebra. The cardiac signs in this instance did not appear until nearly two months after the accident and developed simultaneously with the signs in the cervical vertebræ. Symptoms having an anatomical and functional basis are sometimes intimately linked in the reverse sequence. We may have primarily severe anatomical disease, but frequently with it we have manifestations of very severe functional disturbances which must have their basis in nerve structures more remote than the apparent anatomical lesion. We commonly

[1] *Gazette hebd. de méd. et de chir.*, 1884, p. 657.

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see in the early stages of tuberculosis a rapid heart rate which we interpret as being due to toxins of the tubercle bacillus or enlarged tuberculous glands in the mediastinum.

Martius, in his monograph on tachycardia, criticized the attempts to account for the rapid heart rate as a disturbance of the balance between the vagus and cardiac accelerator nerves. The basis of this criticism is the failure to produce paroxysmal tachycardia by severing a heart from its inhibitory fibers. Martius further states that if tachycardia be due to vagus disease, such as must result from direct pressure of mediastinal glands, then the tachycardia could not be paroxysmal in type, but must be constant. Martius' position is not confirmed by the clinical experiences of others. There are a number of cases reported by other observers and two instances have come under personal observation in which paroxysmal tachycardia was implanted on a constant tachycardia resulting from tuberculosis of the mediastinal glands. We find also that functional disturbances in regions of the vagus supply (other than the heart) may be paroxysmal in character, when pressure from the mediastinal glands is the cause. Neusser reports a case in which paroxysms of meteorism accompanied the paroxysmal cardiac symptoms. Another instance of this character which came under the writer's observation was in a girl, aged eight years, who for two years had marked signs of tuberculosis of the anterior cervical and mediastinal lymph glands. The autopsy revealed a mediastinum packed full of tuberculous glands in various stages of caseous softening. For two years the child had been subject to attacks of spasmodic asthma which were very severe and came as a rule with abrupt suddenness and lasted from thirty minutes to an hour, and then ceased as abruptly as they appeared. After these attacks the child ran about and played as she had done up to the time of her asthmatic seizure. During the last two years of life, this child had an attack about once a month. In the intervals she had slight cough. She was pale and poorly nourished, but otherwise nothing attracted the parents' attention. The writer saw the child in her last asthmatic attack. The lower border of the lungs reached to the tenth rib in the axillary line. The child was profoundly cyanotic and presented all the objective signs of asthma with acute pulmonary emphysema. The cardiac rate during the attack was 140. Quite suddenly all respiratory distress ceased. The asthmatic breathing was replaced with easy inspiration and expiration, and quite as suddenly the lower border of the lung ascended two inches. Within a few seconds there was sudden transition from severe bronchial asthma with emphysema to perfect respiratory comfort and normal lung volume. All traces of cyanosis disappeared in the fraction of a minute. The heart rate, however, remained the same and the child seemed very much prostrated. Sudden death occurred half an hour after the respiratory distress ceased.

Paroxysmal disturbances of cardiac rate and rhythm are sometimes superadded symptoms in the course of organic diseases. Coincident with the gastric crises of locomotor ataxia, paroxysms of tachycardia may occur. A heart rate of over 200 per minute may suddenly develop, which persists from a half to twenty-four hours and ceases as abruptly as it commenced. Disturbance in the cardiac rhythm is of course one of the commonest clinical aspects of valvular disease, although in addition to the usual disturbances of rate and rhythm we may sometimes have paroxysmal tachycardia. This has been observed in patients with mitral stenosis and aortic insufficiency.

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The method of onset of attacks in such cases is very similar to that in essential paroxysmal tachycardia and tachycardia from reflex sources. In disease of the myocardium we may have either an increase in the rate or bradycardia, such as occur in myocarditis of acute infectious diseases and in myocarditis of the senile heart, but in addition to the moderate tachycardia so common in myocardial diseases, there are also paroxysmal attacks of tachycardia which begin with a few pulses of the vagus character or extrasystole, and are succeeded directly by a heart rate as high as 240. A woman, aged fifty-six years, presented a very characteristic clinical picture of myocarditis which followed a lobar pneumonia six years before. The signs of myocarditis were increased volume of the left and right ventricles, dyspnœa, and tachycardia on slight exertion. Although she was quite anxious and fretted much over the limitations which her myocarditis placed upon her, the phase of the disease hardest for her to endure was paroxysmal tachycardia, which recurred during the six years at intervals of one to two months. The onset was very abrupt in all the attacks. The abatement, however, was very gradual and lasted over a period of about one-half hour. The duration of the attacks was usually as long as ten hours. With the exception of the gradual abatement the attacks were identical with paroxysmal tachycardia from other sources. In all of the instances cited above—namely, disturbances of rate and rhythm from the cerebral cortex, from the basal ganglia, from the cervical cord, from the vagus trunk, and from the myocardium itself, there is a certain constancy in the clinical picture which makes it appear as though they have in common an ultimate nervous mechanism, probably through the bulbar centres. All of the cited cases are reflex with the single exception of the tachycardia accompanying myocarditis.

The question of autonomy of the heart being myogenic or neurogenic is inseparable from the discussion of changes in heart rate and rhythm from any cause. The champions of the myogenic theory have shown how independent the heart may be of all connection with the central nervous system, as is shown by an animal surviving eleven months after all connections of the heart with the brain, spinal cord, and sympathetic nervous system were severed. Wave transmission within the myocardium independent of any nerve contact is apparently shown by the series of sections through the heart's muscle which sever all continuity of nerve paths from the base to the apex of the heart and yet maintains muscular continuity through very narrow muscular isthmi. The embryologists have been able to show that the rhythmic beat of the heart occurs before any nerve structures are found in the heart itself, and Hering and others have shown how the resuscitation of the heart, after removal from the body, seems dependent upon metabolic processes within the myocardium. Anyone who follows the work of the physiological laboratory will be impressed with the fact that experiments so far have not succeeded in quite disposing of nervous structures as a factor in autonomy of the heart. The development of research to the present time shows a tendency to reconcile the two views. We are indebted to the champions of the myogenic theory for the most complete analyses of the direction of the nervous system over the rate and rhythm of heart beat. The cardiac nerve supply is composed of centripetal and centrifugal paths. All of the known paths are centrifugal with the exception of the depressor, which is centripetal and has its reflex arc through the vagus. The accelerator centres

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have been located in the medulla and the inhibitory centre is found near the calamus scriptorius in the frog. For the cat the inhibitory centre has been located by a puncture a little to one side of the median line about the middle of the medulla. The accelerator and inhibitory impulses come through the sympathetic and vagus centrifugal paths respectively.

The question of the role of Remak's, Biedert's, and Ludwig's ganglia in the automatic rhythm and correlation of function of the chambers of the heart is one which will necessarily interest the student who wishes to consider forms of cardiac arhythmia. Whether the ganglia are responsible for transmission of impulses within the heart and whether they control a reciprocal action of auricle and ventricle with the significance of nerve centres or whether they are terminal structures through which the reflex control of the heart is maintained is an unsolved problem. The champions of the myogenic theory have adopted a nomenclature for certain modifications of cardiac activity which are employed to great advantage in classifying some of the disturbances of rate and rhythm of the heart. This very minute direction of the heart by nerve agency has been classified into chronotropic, inotropic, dromotropic, and bathmotropic influences. In the present state of our knowledge of the mechanism of these influences, they have for the clinican a purely symptomatic and not an anatomical significance. The chronotropic influences are all those which modify the rate of the heart; the positive chronotropic influences increase the rate and the negative chronotropic influences diminish it. Positive inotropic influences increase the force and excursion of the heart muscle in its action and negative inotropic influences diminish its force and excursion. Dromotropic influences are those which modify the transmission of muscular waves within the heart. Positive dromotropic influences facilitate the transmission of waves and negative dromotropic influences retard the transmission of muscular waves. Positive bathmotropic influences increase the sensitiveness of the myocardium in response to stimuli, that is, a positive bathmotropic influence will render the heart susceptible to a stimulus of lesser intensity and a negative bathmotropic influence renders the heart less susceptible to stimuli. Although the myocardium may enjoy an autonomy independent of its nerve supply, we see the work of the heart in its minutest detail is assigned to the direction of the nervous system. It is very desirable in clinical study to locate the source of these influences in the myocardium, extracardial nerves, the basal ganglia, the cerebral cortex, or remote nerve terminations in the abdominal and pelvic sympathetic distribution. To arrive at a clinical consideration of these phenomena we still accept a purely symptomatic classification of tachycardia, bradycardia, and arhythmia.

TACHYCARDIA.

An increase in the heart rate may occur in some stages of the progress of nearly all pathological processes; in the usual form of rapid heart or polysystole the increase in the rate is accomplished at the expense of diastolic time in the cardiac cycle. The long pause is much shortened, but the shortening of time between the systolic and diastolic sounds (namely, the short pause of the cardiac cycle) is not apparent. We may have a great increase in the heart rate, but on auscultation we are able to differentiate phases of

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the cardiac cycle by the intrinsic character of the two sounds and spacing of the silent phases. By embryocardia we understand not only an increase in the heart rate, but also a modification of the heart sounds and spacing of the silent phases. In embryocardia the systolic and diastolic sounds are identical in character and there is a shortening not only of the long pause, but also of the short pause, and the two have the same length. This condition in the heart is analogous to a vasomotor disturbance in the arterial pulse. Embryocardia is to the heart what pulsus parvus et celer of vasomotor exhaustion is to the artery. If this is a legitimate physiological conception of the heart's action the term tachycardia is very suitable for this phenomenon. The distinction between polysystole and embryocardia is very clearly brought out in instances of rapid heart rate, such as we may see in pressure neuritis of the vagus on which is grafted the phenomenon of paroxysmal tachycardia. So long as the heart's rate is maintained at 140 or 160 we are able to identify the phases of the heart sounds by their character and by the spacing of the silent phases. If an attack of paroxysmal tachycardia should appear, all this differentiation is effaced and we have the phenomenon of embryocardia. For the production of embryocardia we must have a marked shortening of the refractory period of the systolic phase of the heart and shortening of the compensatory pause. Thus we see tachycardia with embryocardia exhibits phenomena which correspond to a prolonged series of extrasystole.

Medical writers have endeavored to differentiate between primary or essential tachycardia and reflex tachycardia. If we use the term reflex as our knowledge of physiology of the cardiac nerve supply will permit, it is possible in the writer's clinical experience to find few cases of paroxysmal tachycardia which were not reflex in origin. We must conceive all influences from the cortex of the brain as reflex as well as influences which come from the distant systemic nerve supply. Paroxysmal tachycardia is clinically inseparable from embryocardia. The duration of attacks varies from a few minutes to two months. The onset is sudden and the termination is equally abrupt. The patient will often have a premonition of impending tachycardia by an occasional extrasystole or intermission. These occasional warnings may occur over a period varying from a half-day to a few minutes, and paroxysms often begin without the slightest premonition. The onset is characterized by subjective symptoms which accompany a vagus pulse. There is a feeling of oppression over the precordial area, a sense of numbness and weakness in the left arm, and a feeling which is described as a sudden flow of blood to the head. Then a throbbing feeling over the heart. The patient feels his pulse and finds a furious tachycardia has commenced. The manner of onset and cessation is very sudden in all cases of tachycardia which we can conceive as having their origin in the medulla. A gradual abatement does not characterize tachycardia which is myocardial in origin. Even where vagus pressure is the cause of tachycardia and rapid heart rate is constant throughout the course of the disease, we may have paroxysmal attacks which are analogous to the crises in diseases of the central nervous system, such as tabes. The case of spasmodic asthma in the child with tuberculous mediastinal glands may be regarded as a pulmonary crisis of vagus disease. Cardiac crises in the course of vagus disease is a closely related conception. Two cases of paroxysmal tachycardia, both of which occurred in physicians, elucidate this point. One occurred in a man who in every

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other respect was perfectly healthy. Physical examination and the personal history did not reveal the slightest suspicion of any organic or functional disorder. The other occurred in a man who had tuberculosis in both lungs with enlarged tuberculous mediastinal glands and tuberculosis of the genito-urinary tract. This man conducted an office consultation practice, and at times was interrupted in his work by paroxysms of tachycardia which recurred at intervals varying from one to two months. He would retire to a private room and with the aid of an assistant stand on his head. The tachycardia ceased a few moments after he was inverted. The first patient adopted the same practice and found the attacks ceased directly be was in the inverted position. Both were relieved by the same procedure, although one had gross pathological lesions in the mediastinum and the other was free from any pathological signs. If there is any method of differentiating between a myocardial or essential tachycardia and one which has its origin in the central nervous system, it is the therapeutic test. If tachycardia can be allayed by stimulating the vagus trunk or by exciting the medullary inhibitory centre, then the source cannot be in the myocardium. If these measures are futile, the evidence goes to show that the abnormal stimuli originate in the myocardium, either at the junction of the veins with the auricle or in the atrio-ventricular bridge.

Nothnagel[1] conceived the cause of paroxysmal tachycardia as analogous to the nervous state in petit mal and epilepsy. He regarded the attack as being a temporary slumber of the vagus centre. Cases which are relieved by measures which affect the vagus centre are quite consistent with this conception. It is impossible to reproduce the picture of tachycardia by any experimental procedure on the vagus or the accelerator. It seems as though the symptoms of paroxysmal tachycardia must have their origin in some molecular change within the medulla. Frequently the attacks are accompanied by other bulbar symptoms, such as spasm of the glottis, stridulous respiration, dilatation or contraction of the pupils, polyuria, and sweating. Vomiting may occur either during the attack or at its conclusion. Rose[2] described a patient whose attacks lasted a week or more. The approach of the end of an attack was always preceded by a herpes labialis on one side.

During the attacks of tachycardia the precordial region is moderately sensitive. The arms feel heavy, and although the sense of exhaustion is only moderate in the beginning of an attack, there is always a strong impulse to occupy a horizontal position. The signs of stasis do not appear early in an attack, rarely in the first twenty-four hours; but if the attack is prolonged we may have the complete picture of myocardial failure, dilatation of the heart, distended veins, pulmonary stasis with albuminous or bloody expectoration, hepatic enlargement, albuminuria, œdema of the legs, and cyanosis. Cases which present all of this train of symptoms corresponded to Bouveret's conception of essential paroxysmal tachycardia, and although the duration of life may be very many years, death ultimately comes in the course of an attack of tachycardia.

One patient with associated myocarditis experienced great discomfort from palpitation, with a heart rate of 140 after moderate exercise; but during the paroxysms of tachycardia with a heart rate of 220 there was not the

[1] *Wiener med. Blätter*, 1887, Nrs. 1, 2, und 3.
[2] *Berlin. klin. Wochenschrift*, 1901, Nrs. 27 und 28.

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slightest subjective palpitation. The sense of palpitation is dependent on hyperdiastole, not on the rate of contraction. These patients may have vascular palpitation, which is determined by the rise and celerity of the pulse wave. The pulse may be of the celer type with considerable excursions of the artery. It may be hyperdicrotic or extremely small and monocrotic. These deviations in the character of the pulse depend upon the dilatation of the splanchnic vessels and the volume of the pulse wave. The patient may be flushed or pale, depending entirely upon the relative distribution of the blood to the periphery and splanchnic area. Cyanosis is pronounced in the prolonged attacks accompanied by failure of the blood hydraulics.

Treatment.—Treatment of the individual attacks is directed either toward stimulation of the vagus, stimulation of the inhibitory centres, or modifying the blood distribution by employing pressure or the aid of gravity to empty the splanchnic veins. The vagus may be stimulated either by direct compression or by the galvanic current. Bulbar stimulation may be attempted by the use of a spray of ether or ethyl-chloride over the nape of the neck. By placing the patient with the head and trunk downward we not only drain the splanchnic regions, but produce a passive hyperæmia at the base of the brain and thus stimulate the vagus centre. Compression of the abdomen has been employed successfully by wrapping a towel tightly about the abdomen. In this manner uniform and strong pressure was exerted on all sides of the abdominal cavity. Patients frequently find they can stop the attacks if they take a deep breath, close the glottis, and make a strong expiratory effort while lying down with the head low. By this method they accomplish the very results which are attained by the inverted position or abdominal compression. Local application of ice-bags and leeches over the precordial area seem to be of little or no service, although commonly employed. Drugs are of very doubtful value and various men report success with drugs which cause both vascular contraction and drugs which cause vascular dilatation. Quinine in large doses, ergot, and adrenalin are of the first class. Nitrite of amyl and nitroglycerin have been employed in the second class with reported success. Digitalis seems the most rational drug to employ when the mechanical therapy above described fails to give relief.

BRADYCARDIA.

The frequency of bradycardia varies greatly in the experience of physicians; from 4 to 17 per cent. of the total number of patients are reported by different men. Some writers report bradycardia as more common in men than in women. From reports of various writers the proportion of women to men is all the way from 6 to 50 per cent. Bradycardia may result from reflex and direct stimulation of the vagus centre, from irritation of the vagus trunk, or it may originate in the heart itself. An approximate differentiation between these various sources of bradycardia may be shown by the employment of atropine, which paralyzes the vagus terminations in the heart. Given a case of bradycardia which will show a marked increase of the heart rate after the administration of atropine, we can assume the cause of bradycardia is extracardial. Intracardial bradycardia may be slightly affected by atropine if the normal negative dromotropic influence is intact. From experience, however, we find bradycardia associated with myocarditis is little affected

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by atropine. In the Stokes-Adams syndrome a combination of the myocardial and extracardial causes may exist. Sclerosis of the coronary arteries and the bulbar vessels may give the negative dromotropic effects at the atrio-ventricular bridge (heart-block) and stimulation of the medulla from anæmia.

Bradycardia which accompanies acute infections may have two sources of origin—namely myocarditis and infectious vagus neuritis. Myocardial bradycardia may be due to negative bathmotropic influences from muscular exhaustion or it may be caused by negative bathmotropic influences due to the effect of some toxin at Remak's ganglia. Negative dromotropic influences may also cause a slow pulse if there be poor muscular nutrition, degenerative myocarditis, or toxic effects on the heart muscle. Negative dromotropic influences resulting in heart-block may be myogenic or neurogenic in origin. The mere existence of heart-block does not exclude a possible vagus origin of bradycardia. Atropine when given in considerable doses to young and vigorous persons will increase the heart rate from 20 to 50 beats in a minute. When given to older persons the increase in the heart rate is not so pronounced. This does not necessarily imply a loss of efficiency in the myocardium, but a diminution of irritability. Bradycardia due to heart-block at the atrio-ventricular bridge will not be affected by atropine. In such an instance the automatic rhythm will be perfectly normal at the auricle, but transmission to the ventricle is impaired. Atropine, therefore, may not affect ventricular bradycardia if the automatic rhythm of the auricle is normal. It is conceivable that atropine may be of some service in forms of myocardial bradycardia by diminishing the vagus-negative dromotropic influence. Therefore, atropine cannot be dogmatically forbidden in myocardial bradycardia. Given a case of slow pulse one must not only take the precaution to determine if the number of heart beats coincides with the pulse, but also, if possible, whether there may not be two or more contractions of the auricle to one of the ventricle. In many instances of rhythmic bradycardia we see in the external jugular vein, or bulbus venosus, centrifugal pulses which betray two or three contractions of the auricle to one of the ventricle. Many of the most pronounced cases of bradycardia with a heart rate of 16 or 18 to the minute have occurred in disease of the coronary arteries. These are the very cases in which conditions are most favorable to heart-block and may not cause a genuine bradycardia of the entire heart. Very many of these are merely ventricular bradycardia from heart-block and are not bradycardia from negative bathmatropic influences. Under the latter conditions there will be an absence of signs in the jugular veins above described.

Bradycardia originating from the central nervous system is in most instances reflex as well as that which originates reflexly from more remote nerve distribution. A few exceptions are cases caused by bacterial emboli in the medullary vessels, disease of the vessels supplying the medulla and bulbar affections in diseases of the cord and brain. Any process which causes an increased intracranial pressure may cause bradycardia. Bradycardia may occur in melancholia, hysteria, and neurasthenia, and is sometimes found in syringomyelia, combined systemic disease of the cord, and tabes dorsalis. Bradycardia may also occur from pressure on the cervical cord due to neoplasm, hemorrhage, or disease of the vertebra. Van Noorden reports 11 cases of hysteria and neurasthenia, in 6 of which there were symptoms

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from the stomach or larynx with bradycardia. Wallenberg reports a case of bradycardia which was apparently due to severing the accelerator fibers leading to the sympathetic from the third dorsal nerve. A policeman while making an arrest received a stab wound on the left of the third dorsal vertebra. Directly on receiving the injury, he observed there was something wrong with his heart. He had anæsthesia in the regions supplied by the third dorsal nerve and bradycardia. The bradycardia ceased with healing of the wound.

In company with E. Carter, of Cleveland, the writer saw a young, vigorous man suffering with a recurrence of acute articular rheumatism. The right knee-joint was distended with fluid, but not painful. With the second attack there was no elevation of temperature. Simultaneous with the return of arthritis in the knee-joint, an acute phlebitis of the right femoral vein developed, which apparently involved the venous trunk above Poupart's ligament. There was intense pain over Scarpa's triangle and deep in the right inguinal region above the bend of the thigh. While this pain was at its height the patient developed an alarming bradycardia of 30 per minute, with arhythmia. The arterial pressure was low and there was no discomfort referred to the precordial region. There was no dyspnœa, cough, or pain in the thorax and no subsequent subjective or objective signs of pulmonary infarct. In the absence of all signs of pulmonary or crossed emboli the only explanation was reflex vagus inhibition through the abdominal sympathetic from branches of the superior hypogastric plexus. The bradycardia persisted for about ten hours. The heart rate gradually increased to 70 in the course of a few hours and remained so during convalescence. There was no recurrence of pain after the bradycardia ceased. The thickening of the femoral vein was distinctly palpable. This explanation is not far-fetched, if we consider that cardiac inhibition results from stimulation of the central end of the splanchnic and the observations referred to by Kisch, who cites instances of sudden death which occurred during parturition and slight operations on the genitalia. Hegar (cited by Kisch) observed that slowing and arrest of the heart beat were caused by pulling on the ovaries and by removing them. The path of reflex inhibition suggested by Kisch is through the abdominal sympathetic by way of the superior hypogastric plexus. My colleague, Hunter Robb, of Cleveland, has had several experiences which go to confirm this reflex path for the production of bradycardia. After abdominal section and operation on the Fallopian tubes he observed bradycardia as low as 20 per minute in several patients.

Bradycardia from the vagus trunk may occur with hemorrhage in the vagus sheath, pressure from primary or secondary growths, and inflammation of the vagus in multiple neuritis or vagus neuritis from toxic sources, *e. g.*, lead poisoning and the vagus neuritis which follows the acute infections, of which diphtheria and influenza are the most frequent. A vigorous young workingman, aged twenty-two years, gave a history of slight chill with fever and headache for several days before the following symptoms appeared. About four days after the fever subsided he was seized with severe pain in both sides of the neck, which was referred along the sternomastoid muscle; rotation of the head and bending the head to either side caused severe pain. Though he was going about, the heart was arhythmic and had a rate of 60. The heart was not dilated and the patient was not dyspnœic. The heart sounds were clear, but there

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was a distinct lengthening of the short pause and the aortic closure was accentuated. Moderate pressure over the vagus at the middle of the anterior border of the sternomastoid muscles on both sides slowed the heart rate to 30 per minute and increased the arhythmia. This caused the patient no discomfort, but if the sternomastoid muscles were compressed at their middle portion the patient complained of severe pain. The pupils were equal and reacted normally to light and accommodation. There were no other signs of disturbed vagus innervation. The symptoms all disappeared in about two weeks' time.

This tracing from the radial artery was procured from a man with diabetes mellitus, moderate arterial sclerosis, and a history of syphilitic infection twenty-five years ago. The sudden intermission and subsequent slowing of the heart rate was caused by giving him a single short dig with the finger over the site of his vagus trunk in front of the middle of the sternomastoid muscle of the right side. Firm pressure over this site caused such cardiac inhibition that it seemed dangerous to employ prolonged pressure. After treatment for both diabetes and syphilis was used for several months, the vagus no longer responded in this manner. This was probably a diabetic neuritis of the right vagus nerve. All cases of vagus neuritis, however, do not respond to mechanical irritation. This probably depends on the portion of the vagus trunk involved. A woman, aged fifty years, had stenosis and insufficiency of the aortic orifice from an old endocarditis. She suffered for

FIG. 24

Tracing from the radial artery.

ten days from a severe facial erysipelas which involved the subcutaneous tissue and caused great œdema of the face and neck. On the tenth day of the erysipelas the temperature was 101° and the pulse rate, which had been as high as 100, sank to 40. The pulse was regular and rhythmic and there was no visible pulsation in the jugular veins, nor could any tracing from them be procured. A hypodermic injection of $\frac{1}{100}$ grain of atropine was followed in fifteen minutes by an increase of the heart rate to 70. Pressure over the vagi did not affect the heart rate. At the same time genuine bradycardia developed in this patient. She had about five stools a day, which were thin and mixed with a large amount of blood. The intestinal signs were not accompanied by any discomfort or meteorism. The presence of vagus neuritis without the usual response to mechanical stimuli over the accessible portion of the vagus suggested that the intestinal signs were due to trophic lesions in the intestine caused by involvement of the vagus ganglion. An inflammation at that point would explain the cardiac and intestinal symptoms and at the same time explain the failure to modify the heart rate by pressure over the nerve trunk in the middle of the neck. The intestinal symptoms and the bradycardia both disappeared in a week.

Huchard cites a case of bradycardia in pericarditis described by Graves,

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in which the heart rate was reduced to 36 per minute. There are two sources for such a bradycardia. It may originate from vagus neuritis secondary to mediastinitis or from myocarditis secondary to epicardial inflammation. Neusser reports a case of bradycardia due to auto-intoxication, which was attended with acetonuria and strongly simulated meningitis. The bradycardia promptly disappeared after liberal doses of calomel. Bradycardia may occur in a number of intoxications, such as by lead, digitalis, muscarin, picric acid, and physostigmine. Nicotine in pharmacological experiment is found to slow the rate of the heart, but we do not see this phase of nicotine poisoning in smokers, as the patient does not consult his physician until the later effects of rapid heart and arhythmia appear. In the course of infectious disease there are several sources of bradycardia to be considered: the infectious vagus neuritis, myocarditis, and toxins which may affect the heart muscle or its nerve supply. Roger[1] described endotoxins in bacteria which caused a slowing of the heart rate and dilatation of the splanchnic vessels, results strikingly similar to those attending irritation of the depressor nerve of the heart. The diagnosis of bradycardia requires first to determine the relation of the arterial pulse to the number of heart impulses and the number of centrifugal pulses in the vein. To learn whether there is a genuine bradycardia, ineffectual heart beats or heart-block, the next procedure will be to look for evidence of disease in the brain or spinal cord and any possible sources for toxic infections or pressure vagus neuritis, and finally we must consider the myocardium and seek for possible sources of reflex stimuli.

The feeling of palpitation in bradycardia may be a very uncomfortable symptom if there is hyperdiastole. If there is no hyperdiastole the patient will discover his bradycardia only on account of some cause other than the heart rate which leads to an examination of the pulse. The mere slowing of the heart rate is well tolerated. Subjective or objective signs from changes in the mass movement of the blood or blood distribution are due to other causes than the mere bradycardia.

Treatment.—The treatment of any case of bradycardia will of course depend upon its origin. If the ultimate cause of the bradycardia cannot be determined, the treatment must be purely symptomatic. If the pulse shows a considerable degree of peripheral resistance, the employment of nitrites in the form of sodium nitrite, nitroglycerin, and nitrite of amyl may cause the symptom to disappear by improving the blood supply to the coronary distribution and the medulla. Atropine will increase the pulse rate if there is a genuine bradycardia due to direct or reflex vagus excitation. When the slow pulse rate is due to heart-block, as occurs in the Stokes-Adams syndrome, atropine will increase the rate of auricular systole, but the rate of ventricular systole is unaffected. Dehio employed atropine to differentiate between bradycardia due to myocardial affections and bradycardia due to extracardial vagus irritation. This does not invariably follow, so a trial of atropine is justifiable in bradycardia from any cause. Warm applications to preserve the body heat should be employed when the surface of the body and extremities are cool. The limbs should be elevated and the head lowered to combat cerebral anæmia. If atropine and the nitrites are not effective, caffeine in liberal doses hypodermically may be employed. Drinking hot coffee in liberal amounts may also be of service.

[1] *Infectious Diseases*, p 444.

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CARDIAC ARHYTHMIA.

Cardiac arhythmia is so protean in its character and method of origin and varies so widely in prognostic and diagnostic significance, that there can be no fixed plan for interpreting its meaning. Any form of arhythmia must be considered in its broadest pathological and etiological relations, before its real portent can be understood. Any disturbance of the heart's rhythm is liable to bring its activity within the consciousness of the individual. This is always uncomfortable and often terrifying to the patient. Whether or not the patient is conscious of his arhythmia seems to sustain no constant relation to the habit of introspection. Some patients who are very much occupied with their own sensorium are quite oblivious to a degree of arhythmia which in other persons causes great alarm. This may, however, depend upon the points to which the patient's attention is directed. The physician's diagnostic art is rarely more severely taxed than in explaining the cause and significance of some cases of arhythmia. It may be due to stimuli of many kinds from the meninges, cerebral cortex, base of the brain and cord. Arhythmia may be a conspicuous sign when there is irritation in the vast region supplied by the great thoracic abdominal and hypogastric sympathetic chain and finally the heart itself or its direct nerve supply may be the sources. This very large range of possibilities brings the clinical study of cardiac arhythmia in touch with the whole known and speculative field of pathological physiology.

Another feature of the mechanism of arhythmia still further complicates its study, and that is the varying results to the heart's rhythm which are obtained both clinically and experimentally at various times by what seem to be identical conditions. Cardiac activity is the expression of coördinate excitation and inhibition in the nerve paths and nerve centres, and when we consider the close anatomical relation of excitory and inhibitory paths and centres and the equilibrium of the automatic centre in the heart itself with the property of the auricle and ventricle to independently assume the rhythm, then we have some conception of the very intricate problem. To appreciate this phase of the subject we have only to read the conflicting reports from experimental studies of vagus influences. Reflex influences on the heart rhythm from every source may at different times have different effects. Myocarditis may increase or diminish the heart rate or cause it to be irregular. Pressure on the vagi from tuberculous disease of the mediastinal glands has been observed to cause paroxysmal bradycardia and paroxysmal tachycardia. Gaseous distention of the stomach may cause genuine bradycardia, heart-block, tachycardia, extrasystole, genuine arhythmia, and the cycle of vagus irritation. These varying signs may occur in the same person at different times and in the same attack a transition from tachycardia to bradycardia with heart-block has been seen. Pelvic diseases have also been observed to give widely differing results in animal experiment and clinical experience.

Besides the factors above mentioned we must in clinical practice consider the share that psychic stimuli contribute to the production of arhythmia. Nervous persons who occupy themselves with the study of their pulse are able to produce arhythmia. Psychical arhythmia is seen in hysterical and hypochondriacal patients to persist continuously, and during periods of great

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mental or emotional distress arhythmia has been observed to be paroxysmal, just as rapid heart and slow heart are commonly seen to assume the paroxysmal character. Mental impressions which are severe although not protracted, and are unassociated with injury or bodily suffering, may be responsible for cardiac intermissions for months afterward. This form of arhythmia is frequently submitted to the physician's judgment in traumatic neuroses which involve a claim for damages. Cardiac arhythmia occurs under these conditions when there is no claim for damages to modify the course of the affection. Meningeal irritation of the early stages of tuberculous meningitis in children is commonly associated with arhythmia and believed to have diagnostic importance in the early stages of vomiting from this affection, but slow heart rate and arhythmia may be caused by reflex vagus irritation in vomiting from any cause. Irritation of the vagus trunk may cause arhythmia, but in such cases it is associated with a diminution or increase in the heart rate. Arhythmia from this source accompanies diseases in the mediastinum and toxic affects on the vagi and infectious inflammations of the vagi. Heubner reported several cases of arhythmia in children following the use of digitalis and opium in small therapeutic doses. Tea and coffee are credited with causing arhythmia, and the writer has had several patients in whom tea and coffee were apparently the cause of moderate arhythmia; at least the arhythmia ceased after coffee was discontinued. Stokes gives an account of two instances of arhythmia with tachycardia which followed in the same day after drinking tea in unusually large quantities. Immoderate drinking of tea and coffee certainly has decided effects on the vasomotor system and increase the force and frequency of the heart beat, and possibly even in small amounts causes arhythmia in susceptible persons. A conclusion in this matter is not justified unless the patient is under observation for a long period and there is opportunity to see how the heart's action is affected by alternately using and quitting tea and coffee.

Reflex stimulation of the vagus nuclei is apparently the cause of arhythmia in affections which involve the region supplied by the great abdominal sympathetic chain and its branches. Huchard reports one case of arhythmia which persisted for three years and was cured directly after a polyp was removed from the uterine cervix. Arhythmia is frequently seen in the post-critical period of acute infectious diseases and is more commonly seen in cases which terminate in crisis than those which terminate by lysis. This may be caused by toxic effects or by an infectious myocarditis; which is responsible in a case lasting a short period it is impossible to determine. It is only in cases which last a long time and subsequently show signs of myocardial dilatation that we can differentiate between these two causes. Up to the present time there has not been a sufficient number of cases studied clinically and pathologically to show the relation between various forms of myocardial disease and certain forms of arhythmia. That disease of the atrio-ventricular bridge will cause heart-block is clearly shown, but beyond this no one has satisfactorily proven that disease of certain portions of the auricle or ventricle have any specific association with disturbances of rate or rhythm of the heart beat. There are cases of marked and constant arhythmia which have been known to exist for many years without causing any functional impairment of the heart's work. Huchard reports three such cases which persisted from childhood to advanced life and Da Costa reports one case which was seen in the twenty-first year of life and was first

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recognized when the patient was six years of age. The writer knows one man, aged forty years, who has a very irregular heart rhythm which was accidentally discovered when he was eighteen years of age. During the past twenty-two years the arhythmia has not varied; there are no other abnormal signs in the heart or circulatory system, and he has conducted a business which requires considerable physical and mental exertion without the least discomfort. Even when arhythmia accompanies acquired heart lesions, patients learn after a time to exclude the arhythmia from their consciousness. The heart-flop, which at first is distressing and alarming, escapes perception after the symptom has lasted for some months. Extrasystole is the form of arhythmia which is most perceived over the heart's region. Genuine arhythmia such as occurs after an infectious disease like influenza is commonly imperceptible to the patient. One patient described two sorts of experiences associated with arhythmia: "One when I feel my heart flop or turn over, and the other is when I notice nothing about my heart, but suddenly start to fall and feel as though I were losing consciousness, when my heart gives a sudden throb and catches me before I lose my footing." The latter experience was due either to a genuine intermission or an extrasystole very early in the diastolic phase and followed by a long compensatory pause.

It would be a valuable aid to the clinical and pathological interpretation of various forms of arhythmia if we were able to differentiate between genuine arhythmia, heart-block, and extrasystole in which the rhythm is assumed by the auricle, and those in which the extrasystole is assumed by the ventricle, but there are several difficulties in the way which thus far have not been satisfactorily solved. Studies of comparative tracings of the venous and arterial pulses and precordial impulses, such as McKenzie and Wenckebach have described, have contributed greatly to our interpretations of arhythmia, but further observations are needed before we can arrive at any definite conclusion in this matter. Precordial impulses are very misleading if we use their tracings to mark the phases of a cardiac cycle, and the difficulty in getting reliable results from tracings of the internal jugular pulses is equally great. The method employed fails to eliminate the factor of centripetal pulses in the internal jugular vein and only partially solves the problem of eliminating from venous tracings the communicated impulses from the carotid artery. In cases of heart-block where there is great dilatation of the jugular veins and the external jugular pulses are clearly free from a centripetal flow and communicated impulses from the internal jugular and carotid artery, such tracings are very successfully made, but finer analyses of these phenomena at the bedside have thus far failed to give completely satisfactory data from which to interpret the various forms of arhythmia. Particularly does this criticism hold in attempts to differentiate between auricular and ventricular forms of extrasystole.

Treatment.—The treatment of arhythmia as a symptom will depend entirely on the underlying cause. When caused by negative dromotropic influences from vagus excitation atropine will serve to increase the heart rate and restore the rhythm, or in certain cases a diminution of the normal vagus tone by the effects of atropine may serve the same purpose. In heart-block due to disease of the atrio-ventricular bridge, atropine will increase the rate of the auricle, but will not affect the ventricular rhythm. Digitalis is efficient in restoring the rhythm of the failing myocardium with rapid rate,

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but our analyses of the subject have thus far offered no further therapeutic indications in its employment to affect the heart rhythm. Cardiac arhythmia caused by some reflex stimuli should be treated by seeking the original cause of irritation.

ANGINA PECTORIS.

Angina pectoris, a disease associated with general and regional vasomotor crises and with nutritive and functional ischæmia of the myocardium, has received as many explanations as there are concomitant symptoms accompanying the attacks. For instance, one writer speaks of Cheyne-Stokes breathing as a symptom which characterizes some attacks of grave angina pectoris. Biot's and Cheyne-Stokes type of respiration may accompany angina pectoris, but there is no interdependence between the cardiac and sensory phenomena and respiratory phenomena. The angina is dependent on disease in the coronary arterial distribution, and the respiratory phenomena are dependent on disease in the arterial distribution to the base of the brain. The respiratory and cardiac symptoms are separate and regional manifestations of the same systemic arterial disease. They are merely concomitant symptoms, and sustain no causal relation to each other.

Another writer wishes to create a class of angina pectoris which is characterized by signs of engorgement in the pulmonary vascular system, a symptom dependent on the accompanying myocardial disease but not characteristic of angina pectoris. Huchard has collected all the explanations which have been offered, and finds as many as eighty.

Angina is associated with an impairment of the blood irrigation of the myocardium. This can arise in several ways:

1. Isolated disease of the coronary arteries unassociated with any affection of the aorta, aortic valves, or systemic arteries.
2. Disease of the coronary arteries associated with systemic arterial disease.
3. Partial or complete occlusion of the lumen of the coronary arteries at their origin on account of disease of the aortic valves or disease of the root of the aorta.
4. Vascular crises in the coronary arterial distribution due to vasomotor influences which are not associated with anatomical lesions of the arteries.

The resourcefulness of the myocardium in meeting sudden demands upon its reserve energy, requires great fluctuations in its blood supply. This wavering blood supply can be secured only by actively varying vasomotor activity. Moreover, the myocardium shares with the gray matter of the central nervous system the highest degree of sensitiveness to an impaired supply of oxygen. From the above classifications there is opportunity for widely differing pictures of angina. An instance of the first class was observed in a man aged sixty years, who had only three attacks of angina prior to his final attack. These occurred at intervals of about six months, and were accompanied by violent pain in the precordial region and dyspnœa. All the attacks followed upon physical exertion. The third attack of pain preceded his sudden death by six months. At the autopsy the heart's muscles, valves, aorta and its branches showed no signs of disease. Both coronary arteries were normal throughout their entire length, with the exception of three-quarters of an inch of the left coronary at the upper portion

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of the anterior interventricular groove, where the branch of the artery was calcareous and the very small lumen was obstructed by a fresh thrombus. There were no traces of old infarcts in the myocardium. In such a case we have to deal with a functional ischæmia prior to the final attack. There was sufficient blood supply to meet the demands of the heart so long as the patient performed no vigorous physical exercise, but when this was performed the heart suffered just as the legs or arms suffer when their respective arteries are sclerosed. The patient with sclerosis of the femoral arteries suffers from intermittent claudication when he attempts to ascend a hill or walk rapidly. There ensues a functional ischæmia associated with pain, muscular cramps and loss of power. The patient with sclerosis of the arterial supply to the stomach is comfortable so long as he is contented with light nourishment and rests after eating, but large meals followed by exercise will induce severe gastric pain with what is apparently an increase of the peristalsis of the stomach wall. Patients who suffer from intermittent claudication of the legs from sclerosed femoral arteries ultimately develop nutritive ischæmia in the form of gangrene. The patient who suffers from arterial disease of his stomach acquires gastric ulcer, from nutritive ischæmia.

The patient with such a sclerosed coronary artery as above described suffers from functional ischæmia for several years, and finally (with complete obstruction of the coronary artery) a nutritive ischæmia ensues over a sufficiently large portion of the heart to cause death. These patients have no increased arterial pressure during their attacks. Vasomotor factors do not share in the production of the symptoms, but their pain is dependent directly on exercise, and can invariably be produced by exercise. Such an angina has a graver significance and demands a more cautious prognosis than the angina which occurs in a patient suffering from general arterial sclerosis and vasomotor spasms.

Angina due to coronary disease without signs of diffuse arterial sclerosis may be very misleading and tempt the physician to underestimate the gravity of the symptoms. The patient's color may not change, there will be no signs of an increased vasomotor resistance, the pulse will show only an increase in rate and lowered pressure, and there may be no disturbance in rhythm. In the Cleveland City Hospital and Infirmary the writer has observed several such cases. The patients were advanced in years and gave a history of having suffered several attacks of pain during the week preceding sudden death. These old people suffered what they believed to be "an attack of wind on the stomach." Indeed, from their conduct one would not believe they suffered intense pain. One old man suffered several attacks of pain during the few days preceding sudden death, but continued to wander about the infirmary halls until the evening he suddenly expired. The autopsy revealed a myomalacia cordis with rupture of the heart wall and several anæmic infarcts in the vicinity of the softened area. Several such experiences led the writer to suspect that these old people tolerate grave lesions of the myocardium better than younger or more vigorous persons, just as gallstones and renal calculi cause less suffering in the old and feeble than they cause in younger and vigorous subjects.

When disease of the coronary arteries is associated with diffuse arterial sclerosis it is common to see very severe systemic vasomotor spasm accompany the attacks of pain, but the pain is apparently not caused by the increased resistance to the heart's work, but because the coronary arteries

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share in the vasomotor spasm. In the Lakeside Hospital, Cleveland, we recently had such a patient whose arterial pressure ordinarily was 180 mm. Hg. During his attacks of pain the pressure repeatedly rose to 300 mm. Hg. The arterial tension and the pain would subside after the administration of large doses of nitroglycerin. On one occasion he was given 1 mm. of a 1 per cent. solution every minute for thirty consecutive minutes before he was relieved of pain. Death was not caused by angina pectoris, but by renal insufficiency. The autopsy revealed marked sclerosis throughout both coronary arteries, but there were no traces of myocardial infarcts and no thrombi in the coronary arteries. All these points contribute to the proof of a systemic vasomotor arterial spasm which was shared by the coronary arteries.

Occlusion of the coronary arteries in disease of the aortic walls and aortic valves is a relatively uncommon form of angina.

A patient seen by the writer twelve years ago in several attacks of angina is still living in a tolerable state of comfort. This patient had an old endocarditis which involved both the aortic and mitral valves. During one attack the arterial pulse became arhythmic and very slow, twenty to the minute. During the bradycardia with arhythmia the jugular veins were distended and pulsated very rapidly. The relative rate of pulsation in the veins and the arteries was not noted at the time, but the slow arhythmic, full arterial pulse and the dilated, rapidly pulsating jugular veins were noted. Reviewing the case to-day, it seems certain that there must have been an acute heart-block with the attack of angina. The results of an embolus in the coronary arteries will vary, of course, with the tolerance of the affected myocardial zone. Should the atrio-ventricular bridge be included in an area of transient ischæmia of the myocardium, then heart-block would be coincident with angina.

Merely high aortic pressure is not sufficient to cause precordial pain. We occasionally see patients with arterial sclerosis who have a systolic blood pressure not far from 300 mm. Hg., but they are quite comfortable so long as they remain at rest. One patient with general arterial sclerosis occasionally has arterial crises without pain, but in these attacks we must assume the coronary arteries are not included in the vascular crises.

A man aged fifty-five years, with cardiovascular disease, seen at intervals during the past six years, has had one attack of transient aphasia, two attacks of transient hemiplegia, and one attack of amaurosis. He recovered from the disability of each attack in less than twelve hours. On one occasion two years ago he was found suffering from mental confusion and in a state of physical weakness which prevented him standing erect. He was in a state of terror, with fear of impending death, but suffered no pain or dyspnœa. The attack came on very suddenly, and the systolic blood pressure was 220 mm. Hg. several hours later when he was comparatively comfortable, but the arterial pressure was certainly higher during the onset of his attack. The arterial pressure in twenty-four hours was reduced to 150 mm. Hg. after the use of saline cathartics, milk diet, and rest in bed. Such vascular crises are probably responsible for *angina sine dolore*, which is described by some authors as occurring in the course of cardiovascular disease.

This was the only instance of the kind observed by the writer, but such vascular crises as this patient had may, in some cases at least, explain the obscure phenomenon of painless angina.

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Angina of vasomotor origin without anatomical disease of the arteries is reported as a result of the abuse of tobacco and of neuropathic origin. The writer has never witnessed an attack of the kind, but from regional vascular crises in the cerebral, retinal, and brachial arteries one is disposed to credit such an interpretation on the part of other observers.

The terms "false" and "true" angina pectoris are unfortunate. The patient who has the symptoms of angina from vascular crises suffers from as true an angina as the patient whose angina is caused by sclerosis of the coronary arteries. The difference lies in the pathological anatomy of the two kinds of angina, but the physiological pathology of the two is the same. In both instances we are dealing with myocardial ischæmia.

Patients suffering from cardiovascular disease with attacks of angina usually present several points of tenderness to pressure; the site of the spinal accessory as it turns over the sternocleidomastoid muscle, the second and third ribs about an inch external to the left sternal border, are the most common points of pressure tenderness. When there is aortitis, the second right interspace at the sternal border is sensitive to pressure, and in many instances the apex of the heart is markedly so. The subjective pain of angina pectoris may have a very wide distribution, the lower end of the sternum usually marks the site of most intense pain, but it may be over the precordial area to the left of the sternum. The pain may extend into the side of the neck over the distribution of the third cervical segment. In the arm the area of pain is most commonly in the distribution of the eighth cervical and first, second, and third dorsal segments.

Epigastric pain and vomiting are very common in angina from myocardial infarcts, but it is very probable that the gastric symptoms described in some cases have been caused by disease of the arterial supply to the stomach, and not to referred pains from the heart. In the past there has not been sufficient appreciation of the role of vascular crises and functional and nutritive ischæmia due to disease of the branches of the abdominal aorta and to disease of the arteries to the brain, so that the respiratory symptoms and nervous symptoms and symptoms from the abdominal viscera which have been so closely linked with attacks of angina pectoris are merely concomitant symptoms, and do not sustain an essential relation to cardiac angina.

Treatment.—This will depend on the presence or absence of vascular signs during the attack. If there is high arterial pressure, nitroglycerin should first be tried in drop doses of a 1 per cent. solution placed on the tongue. The drop should be repeated every minute until the arterial tension is lowered or the characteristic discomfort from use of the drug prevents its further use. Some patients require as much as ten or even twenty drops before the arterial pressure is lowered.

If the tension cannot be lowered by nitroglycerin on account of intolerance of the drug in sufficient doses, then nitrite of amyl should be given by inhalation; some patients tolerate it much better than nitroglycerin. If the attack of pain is not accompanied by signs of vasomotor spasm, hypodermic injections of morphine should be employed without delay. In patients who have had a syphilitic infection, iodide of potash and mercury are, of course, indicated to give relief from syphilitic arteritis of the coronary arteries. But in coronary arterial disease of the senile type, iodide of potash in doses of 5 grains or less should be persistently employed.

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PSEUDO-ANGINA.

Pseudo-angina is a term used to describe attacks of cardiac pain unassociated with pathological lesions of the myocardium, coronary arteries, or aorta. The term is unsatisfactory because the pathological physiology of false angina is not clearly differentiated from the pathological physiology of true angina. The postmortem demonstration of sclerosis of the coronary arteries with thrombi and secondary disease of the myocardium satisfies the inquiring clinician at the autopsy table, but it does not explain all the clinical phenomena encountered in the repeated attacks of angina during a long clinical history. There are several possible sources for the pains of angina, and one of them is spasm of the coronary arteries. The plausibility of this source is supported by the frequent association between angina and vascular spasm elsewhere in the aortic distribution, and the occasional death from angina pectoris when we are compelled by exclusion to employ this explanation for a lethal termination. The phenomenon of vascular crisis in various parts of the body is associated with such grave and palpable results that we can readily imagine the results of a crisis in the vascular supply to the myocardium. Intermittent claudication and cerebral signs, both general and focal in character, are not uncommon in the clinical course of arterial sclerosis. There is nothing in the line of a vascular crisis, however, which brings the nature of the process so clearly to our vision as spasm of the retinal arteries accompanied by amaurosis. Here we have in plain view the only visible arteries of the body clearly exhibiting the procedure which elsewhere in the body must be partially a matter of inference. Regional vascular crises in the veins as well as the arteries are seen as a rare accompaniment of brain tumors and brain syphilis. This very striking clinical symptom, once observed by the writer in the left arm of a patient suffering from brain syphilis, could be well described as a brachial angina. Vascular crisis in the splanchnic vessels in tabetic patients and those suffering from lead poisoning, albuminuria of vasomotor origin in severe mental excitement, all contribute to give to the so-called pseudo-angina or angina vasomotoria a significance which implies grave possible results to an organ so dependent on a blood supply for the performance of its function.

We occasionally meet with cases of angina which have all the characteristics of true angina in the manner of onset, distribution of pain and dyspnœa, and yet these patients some years later are able to perform severe physical labor without discomfort and are quite free from their old complaint. Such cases present all the signs which satisfy a diagnosis of true angina. The patient is seized with violent pain over the sternum and heart area to the left of the sternum. They describe the pain as a violent constricting pain which compels them to remain quiet until it subsides. Dyspnœa is very pronounced and the pain may radiate into the arm and shoulder just as in true angina from disease of the coronary arteries and the aorta. With the employment of cathartics to combat constipation, which may often be the cause of the difficulty, the attacks cease. It seems very probable that many cases of reflex or vasomotor angina are termed such because of their recovery, which is extremely improbable in true angina. But may not the process in some instances associated with heightened arterial pressure be identical with that which we recognize in advanced arteriosclerosis, and the patient

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recover as a result of the therapeutic measures which are directed toward lowering the arterial tension? Clinicians generally recognize the curability of the so-called erethistic stage of arteriosclerosis. Is it not equally reasonable to believe that anginal symptoms which disappear after treatment may have an origin identical with that of true angina? The method of production of reflex vasomotor phenomena through the sympathetic nervous system has not yet gained satisfactory experimental demonstration, but the distribution of pain and tenderness has a more tangible anatomical explanation. The distribution area of pain from true angina may be very large and very remote from the cardiac region. The more common regions of referred pain in true angina are the lower cervical and upper dorsal segment, but the pain may be referred to the epigastrium and even to the area supplied by the hypogastric plexus. We are quite sure of the reflex relation between disturbances in rate and rhythm of the heart and stimuli which originate in these remote organs. The vasomotor processes are very difficult to demonstrate experimentally, but it is not a far-fetched inference to ascribe to reflex vasomotor angina from these remote organs the same physiological process which occurs in true angina.

Huchard cites experiments by Moul, who exposed the heart of a curarized animal and employed artificial respiration. From manometric tracings of the pulmonary artery, it was found that irritation of the gastric or intestinal mucosa and bile tract and kidney caused an increased pressure in the pulmonary artery. The interpretation of these experiments was the existence of a reflex vasomotor arc through the cervical cord and grand sympathetic to the superior thoracic ganglia and cardiopulmonary plexus.

This is also the clinical interpretation of many instances described by French physicians, which are described as the pulmonary form, in which dyspnœa is severe, and accompanied by moderate dilatation of the right ventricle, gallop rhythm over the right ventricle, and accentuation of the pulmonic second sound. In these reflex anginas there is no relation between the severity of the lesion and the reflex phenomena. This must be true if the reflex origin of these symptoms from the abdominal organs really exists, because there is no relation between the cardiovascular signs above described and the grave diseases of the stomach, intestines, liver, and kideny. This form of cardiac pain with gallop rhythm over the right ventricle is described in constipation, meteorism, intestinal parasites, dyspepsia, catarrhal jaundice and gallstones.

It is quite possible that some of the cases of cramp in swimmers are due to vasomotor angina. Bathing in cold water causes cyanosis of the whole body surface, precordial pain, dyspnœa, and tachycardia in some persons. There is a much clearer relation between stomach disturbances and cardiac distress than exists between symptoms from other abdominal viscera and the heart. This phase of the subject will be discussed in a special section.

Diagnosis.—The distinction between angina vasomotoria and angina due to disease of the coronary arteries may be made by eliciting objective signs of disease of the aorta, myocardium, heart valves, or the arteries. The true angina is characterized by the pain being referred more to the substernal than the precordial region, the pain is accompanied by a sense of constriction, whereas the angina vasomotoria gives a sensation of fulness and pressure in the cardiac region. In true angina there is a direct dependence between exercise and the attacks. The vasomotor-angina patient may be capable of

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severe physical exercise in the long interims between the attacks. The treatment of angina nervosa or angina vasomotoria will depend on the etiological factors which may be elicited, such as constipation, errors in diet, indiscretion in eating and drinking, excessive use of tobacco and coffee. The whole manner of life of the patient must be investigated. We must learn not only what the patient consumes, but the domestic relations; the manner in which time is given to work and pleasure may have a direct causal relation of the symptoms. Particularly must signs of the early stages of arterial sclerosis be sought for, because much can be done toward the alleviation of symptoms in such cases and the progress of a grave disease may be arrested.

The pseudo-angina of hysteria presents a very different picture from the vasomotor angina and true angina. The angina of hysteria is merely an incident in this symptom complex. There are other stigmata of the disease present, such as anæsthesia of the glottis, narrowing of the visual fields, stocking anæsthesia, ovarian hyperæsthesia, and other sensory disturbances.

Huchard emphasizes in this relation the existence of tenderness of the intercostal spaces along the path of the phrenic nerves, and also the presence of a small area of superficial tenderness which is located by the intersection of two imaginary lines, one an extension of the line of the tenth rib and the other a continuation of the parasternal line. This point is a little above and external to the umbilicus, and is known as the "bouton de Musey." It was first described by Guneau de Musey as a sign of referred pain to the abdominal region from diseases of the lungs and pleuræ and from neuralgia of the phrenic nerve.

The hysterical patient has repeated attacks in a day, as many as 200 having been recorded. Instead of remaining quiet, nailed to the spot and afraid to breathe, the hysterical patient struggles for air, implores aid by vigorous clamoring, makes vigorous efforts to belch gas, has hiccough or yawns, and gapes to get a satisfactory breath. The last symptom is a common sign in vagus neurosis from any source.

In hysterical angina, precordial pain is but one of the many signs present, whereas in true angina and angina vasomotoria thoracic pain dominates the clinical picture. Pain over the precordial region to the left of the sternum and in the left interscapular space is a very common symptom in neurasthenia and occurs in persons not of a neurotic type, as a sign of physical and nervous exhaustion. Under such conditions, however, the pain does not sustain any fixed relation to physical exercise, and movements are not impeded by its presence. Nor are there any accompanying signs of vasomotor disturbances.

RELATION OF NEUROSES TO CARDIOVASCULAR DISEASES.

With the progress of physiological knowledge, functional diseases grow smaller in number, and it is very probable in future years there will be an assignable physiological cause for some of the cardiovascular symptoms we now class under the head of neuroses or functional diseases. But there are many instances of disturbance of function, change in structure, and finally death of the heart due to purely psychical causes. It is generally conceded that arteriocardiac diseases are found with much greater frequency among persons who in early life are neurasthenic and have many signs of vasomotor

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disturbances. These patients commonly show a wide and tortuous temporal artery. The difficult thing to know in this relation is, if some congenital or vascular defect may not lie at the bottom of the neurasthenia. It seems very reasonable to believe that oft-repeated attacks of tachycardia and arhythmia from gastro-intestinal origin may ultimately cause disease of the myocardium and the coronary circulation. Hayem[1] describes a case of Reichmann's disease with probable scar from an old ulcer obstructing the pylorus. The patient was thin, emaciated, and dyspnœic, with a heart rate of 70. There was cyanosis and œdema of the legs. The right border of the heart was two fingers' breadth to the right of the sternum and there was also asystole. All of these circulatory disturbances disappeared after successful treatment of the stomach. Hayem, with Potain and Huchard and their respective pupils, have all reported numerous cases of this class. They interpret the symptoms as caused by reflex vasomotor spasm of the pulmonary artery, which results in dilatation of the right heart and ultimately general venous stasis.

François Vialand[2] reported a case of heart death with asystole which he interpreted as due to exhaustion through reflex irritation from the ileocæcal region. The patient was a woman aged forty, who had borne five children in rapid succession and passed a large coil of ascaris lumbricoides after severe suffering which lasted seven days. Though there was no dilatation of the heart, the face was slightly cyanotic and the legs œdematous. In this case, however, there was not sufficient precaution to prove the absence of myocarditis by histological examination. Such instances, however, serve to show how strong a tendency exists among French medical men to ascribe grave results to the heart from stimuli originating in the splanchnic area.

Anatomical diseases of the heart have long been regarded as atrophic complications of tabes dorsalis. Numerous cases of death from essential paroxysmal tachycardia are reported, but there is considerable doubt as to this affection being a pure neurosis. There is great probability that congenital hypoplasia and myocardial lesions are the sources of this clinical syndrome. We may in this country take a too mechanical view of heart death and ascribe to myocardial exhaustion results which are due to purely nervous influence. The latter conception of cardiac diseases is found much more frequently among French clinicians, who have contributed much clinical evidence to this view of cardiovascular diseases.

If cardiovascular diseases do result from nervous influence it is apparent that the physician who learns the mental and nervous habits of his patient is in a position to render great prophylactic service. In cases of reflex neuroses the physician should endeavor to learn how much the physical experiences are responsible for the symptoms, and the point from which the original excitation is released. If this latter point can be learned and some procedure instituted which will serve to convince the patient that the cardiac symptoms are purely reflex and not due to grave disease of the heart, much will be accomplished toward a cure of the affliction. We may not understand the exact psychological processes which cause the symptoms, but good judgment on the part of the physician may often direct a mode of living that will enable a patient to escape oft-repeated symptoms which in time may lead to organic disease.

[1] *La médecine moderne*, 1895, p. 445. [2] *Jour. de méd. et chir.*, Paris, 1900, p. 849.

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Stokes[1] in discussing the obscurity of the nature of angina pectoris quotes the following from Latham's lectures: "Think what symptoms are. They are not signs of the disease, but they are direct emanations from it; not things in themselves nugatory, but eminently real. They are natural sensations unduly exalted, or unduly depressed, or variously changed or perverted. They are natural functions, hurt, hindered, or abolished. So that a man may often, with strictest propriety, be said to be ill of his symptoms than to be ill of his disease, and, what is more, to die of his symptoms than to die of his disease."

Grouping of Cases.—There have been attempts to characterize the cardiovascular neuroses from various causes, but with poor results. In all cardiac neuroses there is such a mingling of reflexes from the brain cortex and other organs, the stomach, intestines, or generative organs, that it is difficult to know how much significance each source may have. There is just as abundant clinical evidence of nervous cardiac disturbances of all kinds from the brain as from the peripheral nerve supply.

Extrasystole, genuine arhythmia, bradycardia, tachycardia, hyperdiastole, and eventually dilatation and hypertrophy may all result from purely psychical disturbances. It must not be forgotten that all impulses to the heart from the brain cortex find their way through the bulbar centres and are just as much reflex in character as impulses from the abdominal viscera. It is very improbable that cardiac neuroses from any source are unmixed with reflexes from the cerebral cortex, and the more experience one has in following these cases the more this relation becomes apparent. Emotions of fear from dreading an attack, worry over the obscurity of the underlying cause or a painful sense of guilt, may be factors which will modify results of any reflex stimuli to the heart. There is no one symptom which can be independently linked to stimuli from certain organs. In one patient suffering from cardiac neurosis of gastro-intestinal origin the writer has seen genuine arhythmia, extrasystole, tachycardia, bradycardia, and vagus pulse with hyperdiastole, and all of these various symptoms have been suddenly relieved at one time or another by the eructation of a large amount of gas from the stomach. These attacks gradually grew more frequent during seven years until a method of arresting the tachycardia in its onset was discovered. This gave the patient renewed confidence, and with the exception of very slight attacks at long intervals he was relieved of his cardiac symptoms. The digestive disturbances during all this period remained the same and continued after the cardiac signs practically ceased. So it seems quite justifiable to assume that the cerebral impulses contributed more than the gastric disturbance to producing the heart symptoms. But prior to the renewal of confidence on a justifiable basis it was impossible to recognize the proportion of the psychical factor in the whole trouble.

The attempt to describe the heart disturbances from masturbation as a characteristic clinical syndrome is not justifiable, for here there is the same difficulty of differentiating between psychical affects and reflex disturbances from the sexual organs. The nervous control and direction of the heart is the result of the interaction of excitory and inhibitory reflex influences, and who can estimate the sources of these varying influences during a short period of observation?

[1] *Diseases of the Heart and Aorta*, p. 483.

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The attempt to make a rigid classification of the cardiovascular disturbances in neurasthenia seems quite unjustifiable and unsatisfactory. One author attempts to differentiate between the pulse in the stage of "excitement" and "the latter stage of exhaustion" of neurasthenia, and this too is undertaken with nothing but sphygmographic tracings as a basis. The distribution of the blood in the body is dependent on reflex centres whose equilibrium is in a notoriously wavering state in neurasthenia. It seems a slender basis for clinical grouping of so complex a psychosis as neurasthenia.

Physical Signs.—Physical signs over the region of the heart itself are very misleading in cardiac neuroses. One must always look farther than the heart to prove an anatomical lesion. The evidences of impaired circulation in the lungs, the liver, kidneys, extremities, and central nervous system have the determinating import from a diagnostic standpoint. Murmurs, systolic and diastolic, precordial friction, modifications in the diastolic impulse (gallop rhythm) and all the varieties of arhythmia, bradycardia, tachycardia, and pain may occur in some form of a cardiac neurosis. In prolonged tachycardia, such as the essential paroxysmal type, a genuine passive dilatation occurs. The dilatation is more than a mere active dilatation which is compensatory in character, for it is associated with dyspnœa, pulmonary stasis, cyanosis, and œdema, and yet the heart recovers its normal size so promptly and all its circulatory functions are restored within such a short time that we are compelled to believe a genuine passive dilatation of the heart may exist without a lesion in the myocardium, because such a sudden transition from insufficiency to perfect compensation could not occur under any other than pure nervous conditions. Dilatation and hypertrophy may result from prolonged harmful effects of the emotions. So may hypertrophy result from purely nervous influences, as described by Vaquez's cases of brachial stump neuromata accompanied by tachycardia. Murmurs associated with the heart functions which are not caused by pathological lesions in the valves or myocardium are very obscure in their origin. It is more difficult to understand why murmurs are absent over a heart in any normal case than to conceive their method of origin in pathological cases. Potain's explanation for many of the functional murmurs seems very plausible, as well as for very many precordial murmurs not associated with valvular impairment.

The method of production of the cardiopulmonary murmur is as follows: A piece of aërated lung lies between the contracting heart and the anterior thoracic wall. The lung is compressed between the heart and the thoracic wall so that the air expelled from a tongue of lung thus compressed has a velocity sufficient to produce a murmur. The character of the murmur, its pitch, intensity, and quality will be modified by the force and rate of compression and the contents of the air spaces. If there should be a considerable amount of fluid in the air spaces, the murmur will have a bubbling or even a splashing character. The rasping character of these murmurs over the site of the conus arteriosus of the right ventricle, where precordial movement in an anterior direction is great, often simulates the friction of pericarditis. These murmurs may be so loud as to be heard at a distance from the chest wall. The most striking instance and also the most convincing proof of the manner of production of the cardiopulmonary murmur seen by the writer occurred in a case of bilateral thoracic empyema. Both lungs were displaced toward the median line so that the precordial area was tympanitic and the

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cardiac cycle was accompanied by a loud, rasping friction and bubbling. All the sounds over the tympanitic precordial area had a ringing tympanitic quality which sounded as though they occurred in the presence of fluid and air. The sounds were so loud they could be heard by the unaided ear six inches from the chest wall and attracted the attention of the nurse, who asked, "What is that strange noise over the heart?" The autopsy revealed only the bilateral empyema, with both lungs crowded in front of the heart. There was not the slightest evidence of disease of the heart or pericardium, although the signs led the writer to make a diagnosis of pyopneumopericardium due to some gas-forming bacterium. The peculiar character of the sounds and the postmortem results left no doubt as to the cardiopulmonary origin of the adventitious sounds.

The occurrence of cardiopulmonary murmurs is certainly a common clinical experience and offers a very plausible explanation for many murmurs heard over the heart during excitation of its action. Potain's explanation of the systolic cardiopulmonary murmur is quite satisfactory, but the diastolic cardiopulmonary murmur does not admit of so ready an explanation. Potain believed that the diastolic murmur was due to rapid reëntrance of air into the tongue of lung which was compressed during the systole of the ventricle. An explanation of the endocardial murmur not caused by relative insufficiency of the valves is lacking at present. We are accustomed to apply the terms accidental and hæmic to murmurs which are not caused by some pathological lesion, but the terms have no generic significance.

Modifications in rate and rhythm from nervous influences are very familiar experiences. We know that nervous phenomena may be responsible for chronotropic, dromotropic, bathmotropic, and inotropic influences. This being true, it is not difficult to understand how gallop rhythm, diastolic impulses, and heart-block may be the result of purely nervous influences. With all these possibilities in view, one is reminded of the great caution which must be employed in differentiating between functional and anatomical disease of the heart. There are no fixed rules for differentiating the several signs caused by functional disturbances from those due to anatomical lesions. It is only by considering the general circulatory condition of all the organs of the body that a diagnosis can be made. Besides these adventitious phenomena we not uncommonly find a modification of the heart sounds to which we are accustomed to ascribe considerable diagnostic import in endocarditis. The systolic sound in tachycardia may become loud and high-pitched if the tachycardia is accompanied by dilatation. This is a common occurrence in the essential paroxysmal tachycardia, but is not seen in the reflex tachycardia from gastro-intestinal disturbances. A loud systolic sound over the apex and a loud diastolic sound over the conus arteriosus of the right ventricle are frequent in paroxysmal tachycardia with dilatation. Proximity of the heart to the chest wall will contribute to the intensity of both the systolic apex sound and the second sound over the right conus arteriosus. The shortened and incomplete systole of compensatory dilatation is also a probable factor in accentuation of the systolic sound at the apex.

To differentiate between functional and anatomical diseases of the heart often requires repeated observations over a long period of time with a patient under varying physical conditions and also in some instances with a change of social relations. Domestic infelicity and other disappointments in life are occasionally causes of disturbances of rate and rhythm. Stokes (1853)

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says: "The facility of making a correct diagnosis between functional and organic diseases is not so great as modern writers lead us to believe. And we more often arrive at a just conclusion by instinctive skill, the result of experience and judgment, than by communicable rules of diagnosis."

Palpitation.—This is a term used by patients to express the fact that their heart's activity lies within their own consciousness. In clinical experience it is not synonymous with tachycardia. Many neurotic patients acquire a consciousness of the heart's action when there is nothing abnormal to be detected. These patients seem to acquire consciousness of the normal heart's action just as some patients acquire consciousness of the normal digestive processes in the stomach and intestines. Paroxysmal tachycardia without dilatation of the heart may give the patient no sense of palpitation. A patient with a heart rate of 250 will not complain of the least sense of palpitation. Fever patients do not complain of palpitation. Another patient with a heart rate of 50 complains of palpitation as the most disturbing symptom. A young woman aged twenty-five years, complained of "palpitation" which always accompanied stomach disturbance and belching of gas. The heart rate was 50; the pulse was decidedly of the vagus type, and the systolic sound was loud, low-pitched, and booming in character. There was a strong systolic impulse over the apex, and during the diastolic phase one could palpate a diffuse, soft impulse over the mesocardium. In tachycardia associated with the sense of palpitation there is an active dilatation of the heart. The sensation of palpitation is closely linked to the hyperdiastole of vagus irritation and is quite independent of the heart rate and force of the apex beat.

PAROXYSMAL TACHYCARDIA.

Essential paroxysmal tachycardia is a term credited to Bouveret,[1] who collected the cases published to 1889 and employed this term to describe a train of symptoms which was unassociated with known anatomical lesions or reflex mechanism. Although cardiovascular pathology and physiology have made great progress in the past seventeen years, the term essential paroxysmal tachycardia remains a suitable one for the grouping of these clinical cases, for which there exists no satisfactory physiological or pathological solution. Experimenters have succeeded in reproducing in the laboratory nearly all modifications in the cardiac cycle due to chronotropic, bathmotropic, inotropic, and dromotropic influences which have been clinically described, but a paroxysmal tachycardia has so far not been produced by any experimental procedure on the cardiac nerve supply. By common consent among medical writers, the term tachycardia may be applied to a heart rate above 120, but there is a wide gap between the tachycardia of infectious diseases or exophthalmic goitre and the heart rate of paroxysmal tachycardia. In the latter a heart rate of 240 is common and a rate of 300 to the minute has been observed. When dilatation and asystole occur in this affection, they are the direct result of the tachycardia, whereas in the other affections the tachycardia is secondary to exhaustion from toxic effects as well as the tachycardia. In essential tachycardia the heart rate

[1] *Revue de médecine*, 1889, vol. ix, p. 753.

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always attains a rate of 200 or more within a short time following the beginning of the attack, and with few exceptions the high rate is attained directly the attack begins. Tachycardia is the one symptom which dominates the whole clinical picture and sustains no secondary significance to any other pathological sign. The causes underlying the tachycardia (whatever they may be) are primary and all other signs are results.

In his original classification Bouveret tried to exclude all those paroxysmal tachycardias which were associated with bulbar diseases, affections of the vagi or myocardium, and all those due to reflex stimuli from other viscera and intoxications of all kinds. He did not, however, make a satisfactory differentiation in his cases. This attempt at classification has not been followed by subsequent writers. All of the associated affections which Bouveret attempted to exclude have been included in the collected cases of later students of the subject. A. Hoffmann[1] collected 126 cases with 16 autopsies from the literature; 11 cases showed myocarditis and 2 other cases were described only as dilated hearts without further study of the myocardium. As in every other clinical field in which the pathology is not clear, writers differ in the acceptance and rejection of cases for various reasons. This we must expect when we are dealing with a symptom which has no known physiological or anatomical cause. Hoffmann makes the following etiological classification: mental excitement and fright, 23; head injuries, 3; organic brain diseases, 2; exhausting diseases and toxic causes, 19; disturbances of the abdominal organs, 23; heart affections, 24; physical exertion, 21; and in 21 cases there was no assignable cause. Bradycardia as we see it clinically can be reproduced experimentally by a number of attacks at different points in the neuro-myocardial system, but polysystole such as we see in paroxysmal tachycardia cannot be produced through the nervous system. The only method of approximating it experimentally is by an accumulative series of extrasystoles which result from irritation of the myocardium.

Apparently, we have to deal with the combined results of positive chronotropic and positive bathmotropic influences and from clinical experience, we must believe the origin of paroxysmal tachycardia is due to some combination of these two influences somewhere in the nerve supply of the heart.

The heart stimulus is constant, but the rhythmic cardiac cycle is due to the interaction of inhibition and excitation, which gives the resulting spaces of the several phases of a cardiac cycle. We can compare the flow of energy in the heart's stimulus to a filter under pressure. Although the pressure is constant the flow is interrupted. If the wall of the filter be injured, inhibitory influence is suspended and we have a continuous stream instead of an interrupted flow. This seems to be what really occurs in paroxysmal tachycardia; the inhibitory influence is suspended and, instead of the rhythmic spacing of phases which occurs in more moderate polysystole, we have the phenomena of embryocardia with abolition of the postsystolic refractory period. There is not only a positive chronotropic influence, but also a positive bathmotropic influence which increases the irritability of the heart.

Symptoms.—The first intimation of an attack is the "flop" or "tripping" of the heart. This manifests itself by a throb and sense of oppression over the precordial area and a slight sense of fulness in the vessels of the

[1] *Die Paroxysmale Tachycardie* (Wiesbaden, 1900).

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neck. This is caused by extrasystole which usually precedes the tachycardia. Sometimes the first sensation is that of fainting due to cerebral anæmia, as the extrasystole is very feeble and is succeeded by a long compensatory pause. Several extrasystoles commonly follow and then suddenly the furious storm of tachycardia appears. In one patient, whose pulse was being felt when an attack began, there were three or four extrasystoles clearly palpable before the attack commenced. It is doubtful if extrasystole always ushers in the attack. Patients describe some of the attacks as beginning instantly without the least sense of a "heart-flop" preceding the tachycardia.

The termination of an attack is as prompt as the onset. The rapid rate ceases instantly and is followed by a long pause; then a full strong impulse is felt over the heart, accompanied by a full pulse wave at the wrist. There may be several irregular heart beats and then the normal rhythm and rate are reëstablished, accompanied by a sense of "glow over the whole body." The "flop" and several irregular beats are more constant in the conclusion of the attacks than in the beginning. The relation between paroxysmal tachycardia and Stokes-Adams syndrome has been remarked by several observers. The writer observed the transition from tachycardia to bradycardia in a patient who had been under observation for eight years and who was seen in about twelve paroxysms of tachycardia. The patient has had only one attack of bradycardia. The onset of this attack was with the usual tachycardia of about 220 beats to the minute. After this had lasted about an hour there was a sudden change from tachycardia to bradycardia with arhythmia. There never had been any arhythmia with the tachycardia. The pulse, which to that juncture was rhythmic at 200 or more, suddenly slowed to from 12 to 16 beats in a minute and was very arhythmic. During the bradycardia the external jugular veins and the bulbus venosus were markedly distended. There was no distention of the external jugular veins during tachycardia. The veins pulsated very rapidly, but unfortunately at that time (seven years ago) observations did not go beyond this and the proportionate rate of pulsation between the veins and the artery was not observed. That the veins were distended and pulsated rapidly when the radial pulse was slow, full, and irregular was noted at the time. The change of feeling in the patient was very marked with the advent of the bradycardia with heart-block. The patient had learned to endure the tachycardia, but with the slow pulse there was a sense of anxiety and depression, and every systole was accompanied by a strong throb over the heart area. The bradycardia lasted about half an hour, when suddenly, after the eructation of a large amount of gas from the stomach, the heart resumed its normal rhythm and rate of 76.

Here was an example of a cause producing a series of extrasystoles in the guise of tachycardia which (by some change in the interaction of excitation and inhibition) suddenly transformed the picture of positive chronotropic and positive bathmotropic influences to that of negative chronotropic with negative dromotropic influences.

It is doubtful if all cases of paroxysmal tachycardia are due to a series of extrasystoles. If the classification of paroxysmal tachycardias could be made on this basis we could make one step toward a satisfactory grouping of cases. Such a classification would be more satisfactory than the attempt to classify them on an etiological basis, when we have no physiological understanding of the process.

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Some patients seem to endure their tachycardia with little discomfort and walk about attending to their business with a heart rate of 200 or more. The sense of palpitation is not distressing to some patients; there is then no hyperdiastole. One patient was seized with an attack on a holiday excursion while exploring a ravine a hundred feet deep with densely wooded banks. She climbed out of the ravine and walked from the top of the bank over a freshly ploughed field with a sharp upgrade to a farmhouse a quarter of a mile distant and experienced no dyspnœa during the effort beyond what she would have experienced under normal conditions.

The patient as a rule prefers the horizontal position. There is a sense of constriction in the epigastrium and some precordial anxiety. There is a partial aphonia. The face may be pale, or livid and cyanotic; the jugular veins may or may not be distended. These signs will vary with the vasomotor influences and whether asystole with dilatation has occurred or not. The pupils have been observed to be dilated, contracted, and unequal in different cases, and to vary during a single attack. Profuse sweating is an unusual symptom, although it sometimes occurs. The duration of attacks varies from a few hours to six or eight weeks. The presence of other symptoms will depend upon the endurance of the myocardium. There may be a murmur with the systolic sound or a postsystolic murmur, as described in one of Proebsting's[1] cases. It is more common to find the heart sounds clearly defined even in instances occurring with valvular disease. The murmurs which are present during the usual rate become inaudible with the advent of a tachycardia. Signs of stasis do not appear until the attack has lasted several days and the attack may last many days without any such signs appearing.

When signs of stasis do appear, there may be dilated veins in the neck, cyanosis, pulmonary œdema, with hæmoptysis, swollen liver, and albuminous and bloody urine, œdema of the extremities, and mental confusion. With cardiac dilatation and asystole there is a danger of thrombi forming in the heart chambers and all the possible results from emboli may occur. The existence of such signs, however, do not justify an absolutely bad prognosis, as we learn from Pribram's[2] case of a young woman in whom the pulse rate was at first 220 and then gradually rose to 300. On the fifth day signs of stasis developed. The first sound was replaced by a murmur. Pulmonary stasis, œdema, cyanosis, and dilated heart all pointed to impending death. The patient gave a start and the heart resumed its normal rhythm and rate of 76, and a prompt recovery followed. The pulse in all the patients who have come under personal observation was of small volume, very low pressure and monocrotic, although dicrotism is described in some instances and in other cases the pulse is described as having a maximum pressure little below the normal and of the celer type. Tolerance of these attacks varies in the individual, and from the autopsy reports we should judge that the resistance of the myocardium is the determining factor.

Rose[3] reports a case in a man, aged forty-eight years, who had attacks since his sixteenth year. During his attacks, which lasted several weeks, there was a heart rate of 220, but the arterial relaxation was such that the

[1] *Deutsch. Arch. f. klin. Med.*, 1882, p. 349.
[2] *Wiener. med. Presse*, 1882, Nr. 21.
[3] *Berl. klin. Wochenschrift*, 1901, Nr. 27 und 28.

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patient could count the pulse rate from the throbbing he felt with every arterial pulsation over the whole body. This vasomotor state seems to accompany the tachycardias with grave signs of myocardial incompetency. Pal[1] described one instance of tachycardia during a tabetic crisis with a heart rate of 240 and maximum arterial pressure of 60 mm. Hg, and at this time the pulse was hyperdicrotic. He expresses the opinion that tachycardia which does not cause cardiac dilatation, dyspnœa, cyanosis, or any signs of stasis, is due to the effects of vasodilator influences.

In the light of modern research on cardiac innervation, it seems more reasonable to believe that such cases are due to extrasystole and offer a favorable prognosis compared to the tachycardia which is myocardial in origin. Clinical evidence tends to show that paroxysmal tachycardia may result from diseases of the medulla or reflexly through the medulla, from affections of the vagi and from the myocardial diseases. Whether any of the cases are due (as Pal believes) to vasomotor relaxation in the splanchnic vessels or not is difficult to determine, because it is not settled in any given case if the change of position arrested the tachycardia by blood gravitating out of the splanchnic vessels or if the same procedure did not increase the tone of the vagus inhibitory centre in the medulla and thus slow the runaway heart. Spengler's[2] patient had a heart rate of 80 when lying down and 250 when standing. This is termed orthostatic tachycardia. J. Lardin[3] discovered he could stop his own tachycardia by leaning forward with his arms hanging down. Some persons subject to paroxysmal tachycardia can stop the attacks by standing vertically in a corner with the head down. In others firm bandaging of the abdomen stops the attacks, but it is not absolutely proven that emptying the splanchnic veins gives the relief. Relief from this procedure may come through stimulation of the medulla.

The following case illustrates this point: A woman, aged thirty-five years, has had many attacks of tachycardia during the past ten years, averaging about three or four a year. There has been a very constant relation between nervous or emotional excitement and the attacks. The common sequence of events has been constipation followed by accumulation of gas in the stomach and bowel, several sleepless nights, and then the attack of tachycardia which sometimes began with the "heart flop" and at other times the tachycardia was in full force before any warning of any kind was perceptible. She had learned to bear these attacks with equanimity and no longer permitted them to interfere with attendance on her household duties, as she experienced no severe discomfort. Never before had a paroxysm of tachycardia lasted more than eight hours, but in this instance it persisted twenty-eight hours. The patient had been operated on two weeks before for suppurative salpingitis, and both tubes and ovaries were removed. A daily rise of temperature as high as 101° persisted after the operation. The pulse rate remained between 100 and 120. The preceding day tachycardia commenced without the slightest warning or any unusual experience. The pulse rate was 240 per minute, and so small at the wrist that no tracing could be obtained. The heart dulness was increased one and one-half inches to the right of the sternum and one inch external to the nipple line. There was a large centrifugal pulse visible in the external and internal jugular veins which

[1] *Gefässkrisen*, Leipsic, 1905, p. 51.
[2] *Deutsch. med. Wochenschrift*, 1887.
[3] *L'union médicale*, August 21, 1875.

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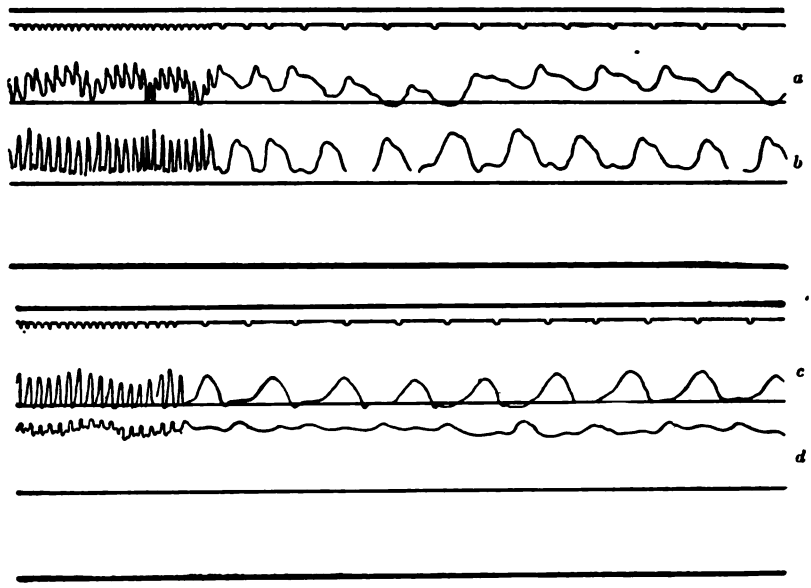
had the same rate as the carotid pulse. It was impossible to determine by inspection the time relation between the jugular and carotid pulses, but the two tracings taken with the Jacquet polysphygmograph show very clearly that the jugular pulse alternated with the heart and with the carotid pulsations. There were no signs of stasis in the liver or extremities. There was no cyanosis or dyspnœa. Embryocardia was well pronounced. The tracings show the correlation between auricular and ventricular contractions as undisturbed. Pressure on the vagi, compression of the abdomen, and holding the glottis closed after deep inspirations had no affect. The patient was then taken out of bed and held with heels up and head down for a minute without result. She was then instructed to take a deep inspiration and "bear down" while in

FIG. 25



a, tracing from the heart; *b* and *c*, tracing from the jugular vein; *d*, tracing from the carotid artery.

the inverted position. In a few seconds the heart rate suddenly changed from 240 to 120, the rate which was in force at the onset of the tachycardia. The tracings and the exact halving of the heart rate at the end of the attack show it to have been caused by the liberation of a series of extrasystoles from the auricle, all of which were transmitted to the ventricle. Vasomotor dilatation in the splanchnic area was probably not the cause of this attack. Had that been the case, inversion alone would have sufficed to arrest the tachycardia. The additional factor (viz., forced expiratory effort with closed glottis after a deep inspiration) was required to stimulate the bulbar inhibitory centre sufficiently to arrest the series of extrasystoles. The heart volume returned to the normal boundaries immediately after the tachycardia ceased.

One patient with paroxysmal tachycardia was fifty-six years of age and suffered from myocardial disease which dated from an attack of lobar pneu-

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monia six years before. She had also phlebitis of both femoral veins after the crisis of the pneumonia. The attacks of tachycardia were rare, in all not more than seven in six years. The heart rate did not exceed 180 and began rather gradually, reaching the maximum rate in about half an hour's time. The rate of 180 persisted as a rule for about ten hours and then gradually subsided to about 140, when the normal rate of 80 was suddenly resumed. There was no cyanosis, dyspnœa, stasis, or polyuria during the attacks. The pulse was not extremely small, but exhibited about the volume to be expected in such a short diastole. There were no evidences of vasomotor disturbances in the extremities or in the splanchnic area. There were no disturbances in the stomach or intestines associated with the attacks, nor eructations of gas at the conclusion of the tachycardia. It is conceivable in such a case of myocarditis that a series of extra systolic impulses liberated at Gaskell's bridge may have been the cause. No clear evidence of ventricular extrasystole could be demonstrated. There was no cardiac dilatation during the attack, and the patient walked about the room with no more difficulty apparently than when the heart rate was 80.

Neusser[1] describes one case of intermittent tachycardia in which the attacks were accompanied by meteorism which he interpreted as originating through the vagus affection due to pressure from tuberculous mediastinal glands. The heart rate during the attacks was only 160, but experience shows that tachycardia from disease of the vagus nerve need not be constant, as is assumed by Martius;[2] spasmodic asthma and pulmonary emphysema may be due to the same cause. For the bulbar origin of some cases of tachycardia the following evidence is offered: polyuria, modifications of the pupil, herpes labialis, vomiting, and vasomotor disturbances in the splanchnic distribution.

Treatment.—The treatment of any given attack suggests first to attempt to influence the heart rate by the position of the body. The very simplest device is to place the patient with the head down and legs elevated, which may be done (where advisable) by laying the patient on a board or hospital litter. Tight bandaging of the abdomen may be employed when the pulse volume is small and there is no dyspnœa, cyanosis, or signs of dilated heart.

An ice-pack or ethyl chloride spray over the nape of the neck may be used with the hope of securing vagus inhibition reflexly from the medulla. Compression of the vagus trunk in the neck at the level of the angle of the thyroid cartilage has been efficient in arresting the attack in several cases. If pressure over the vagus is not successful, galvanization of the vagus may be tried, which according to Huchard should be done in the following manner: A current of from 2 to 4 ma. should be used. The positive pole is applied at the nape of the neck and the negative pole midway on a line connecting the mastoid process with the angle of the thyroid cartilage. Each vagus should be treated two or three times daily and for four or five minutes at each time.

Adrenalin, quinine, ergot, and nitrite of amyl have all been employed as the vasomotor tone of the arteries suggested, but there is little to be hoped for in the employment of any drug.

Protection against the recurring attacks may be favored by leading a life both morally and physically hygienic. Abstinence from tea, coffee, alcohol,

[1] *Ausgewöhlte Kapitel der klinischen Symptomatologie und Diagnostik*, Heft 1, p. 38.
[2] *Tachycardie*, Stuttgart, 1895

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and tobacco should be strictly observed. Any dyspepsia of gastric or intestinal origin should be carefully investigated. Many attacks of paroxysmal tachycardia have their origin in gastro-intestinal disturbances. In this relation may be mentioned one of the earliest cases described, namely, that of Cotton,[1] reported in 1867. This is referred to in literature as cured by the expulsion of a tapeworm. Cotton's case was reported four weeks after the tapeworm incident, and in the patient's history the fact is mentioned that he had previously gone six months without an attack.

STOKES-ADAMS SYNDROME.

The Stokes-Adams syndrome is a group of symptoms which may involve crises in the vascular supply of the brain and medulla and myocardium, and negative chronotropic and negative dromotropic influences originating somewhere in the tract of the vagi, also negative dromotropic influences due to disease at the atrio-ventricular bridge, thus implicating that portion of the myocardium which passes from auricle to ventricle through the atrio-ventricular sulcus. Or there may be negative bathmotropic and chronotropic stimuli manifested at the auricles where the constant stimulus is believed to originate. The term "Stokes-Adams" is applied to certain symptoms and not to a definite pathological process. The causes which give rise to the symptoms may produce their manifestations through irritation of the medulla, upper cervical cord, and vagus trunk, or there may be in addition to the purely nervous influences some lesion in the myocardium which contributes to the slow heart rate and arhythmia commonly present. But bradycardia is not responsible for the cerebral symptoms which accompany the paroxysms. The symptoms vary with the disease of which they may happen to be a manifestation. The clinical picture of pressure on the medulla or upper cervical cord would differ widely from that of sclerosis of the brain arterial supply with chronic interstitial nephritis and sclerosis of the coronary arteries with secondary disease of the myocardium.

The symptoms are both cerebral and cardiac in origin, although bradycardia and arhythmia are the most striking features in many cases. Nervous influences may cause a bradycardia or rather slow pulse in several ways. There may be negative chronotropic or negative bathmotropic influences applied to the supposed seat of origin of cardiac rhythm, namely, at the junction of the veins with the auricles, or on account of negative dromotropic influences at the atrio-ventricular junction heart-block may result, and although the auricle continues a normal or rapid rate, the systolic wave is blocked at the atrio-ventricular junction and the ventricle does not share in the systole. This procedure can be distinctly seen with the fluoroscope. The contractions of the right auricle can be clearly seen and during the block the ventricle is seen to gradually enlarge, and with a complete heart cycle the systole of the ventricle can be clearly seen to succeed the systole of the auricle. So we may have a bradycardia from purely nervous influences which involves auricles and ventricles or a bradycardia which involves the ventricle only. In both conditions of course there is a slow pulse. The real problem, so far as the heart is concerned, is to determine whether we are dealing with a

[1] *British Medical Journal*, June, 1867.

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genuine bradycardia which involves both auricles and ventricles, or heart-block, in which the rhythm of the auricles is maintained, but the ventricle fails to follow. The other problem to determine is where the nervous stimuli arise, in the brain, medulla, cervical cord or vagi, and whether these stimuli arise from disturbances in the vascular supply to these parts or from pressure or intrinsic disease of these structures.

By far the most common association of the Stokes-Adams syndrome is with arterial sclerosis, and in this affection the three organs which suffer mostly from secondary effects are the heart, brain, and kidney. Vascular crises in different parts of the arterial supply are common in this disease. Besides the results of vascular crisis in the arterial supply to the brain there may be many symptoms constantly present. Sclerosis of the coronary arteries commonly results in secondary diseases of the myocardium, which may cause a genuine bradycardia and also heart-block. We have the pathological conditions for bradycardia and heart-block constantly present, and also the necessary conditions in the arterial supply to the brain which produce paroxysmal attacks of bradycardia and heart-block. The other symptoms from the brain are very commonly seen in persons with sclerosis of the cerebral arteries. Bradycardia and heart-block are the unusual symptoms found which were first described by Stokes and Adams, and for this reason their names were used by Huchard[1] to designate this group of cardiac and cerebral symptoms which occur in arteriosclerosis. His[2] later recognized the significance of these symptoms in relation to the myogenic theory of the cardiac rhythm (as conceived by Gaskell) and also the role of "Gaskell's bridge" in the embryology and physiology of the heart as described by Stanley Kent.[3] During the past few years there has been an abundance of very convincing evidence from physiological research to prove that the only path for transmission of coördinate contraction waves from the auricles to the ventricles is through that portion of the atrio-ventricular bridge known as the "bundle of His."

This bundle of muscular fibers is traced from a point about 10 mm. beneath the posterior cusp of the aortic valve and continues in a sharp curve over the upper border of the muscular septum between the ventricles and terminates in the muscle of the right auricle and muscular structures in the atrio-ventricular valve. When this bundle is compressed or divided, the auricle and ventricle each assume a rhythm which is independent of the other. So far, however, there is no satisfactory evidence which shows whether the conduction through this bridge is by way of the muscular fibers or nerve paths. This aspect of Stokes-Adams syndrome has given renewed interest in these symptoms, but thus far there have not been a sufficient number of cases studied with all these points in view, so that we do not know accurately the relations which true bradycardia and heart-block respectively sustain to the Stokes-Adams syndrome. We will have to wait until a number of these cases are studied clinically with comparative tracings of the venous and arterial pulses and cardiac impulses, and followed by accurate studies of the myocardium with reference to the origin and transmission of the heart contraction wave.

Symptoms.—The patients are usually past middle life and present other signs of arterial sclerosis. Bradycardia and arhythmia are constantly

[1] *Maladies de Cœur*, vol. i. [2] *Deutsch. Arch. f. klin. Med.*, vol. lxiv.
[3] *Journal of Physiology*, vol. xiv, p. 229.

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present. The heart rate is commonly 40 or thereabouts, but during the paroxysms the rate becomes slower. In one fatal case described by Huchard the rate was as low as 2 to the minute. There is not a constant relation between the cerebral symptoms and degree of bradycardia and there is no reason to regard the brain symptoms as secondary to the bradycardia. A heart rate of 30 may accompany an apoplectic or epileptic seizure, and the same rate with perfect rhythm has been seen in a neurasthenic man who complained chiefly of symptoms due to dyspepsia. Under paroxysmal tachycardia one instance of sudden transition from paroxysmal tachycardia to paroxysmal bradycardia and arhythmia with a heart rate of only 16 to the minute has been noted. There were all the signs of heart-block one sees in the Stokes-Adams syndrome. Yet there was not the slightest suggestion of any cerebral symptoms. There is very strong evidence that the bradycardia of the paroxysms has its origin in negative chronotropic impulses from the cardiac nerve supply either in the medulla or in its path from the medulla to the heart.

The cerebral signs are due to crises in the vascular supply to the brain and medulla. These may vary greatly in character with the severity of the attack and the parts of the encephalon chiefly implicated. The attack may be merely syncopal, epileptic, or apoplectic in character, with stertorous breathing or even Cheyne-Stokes respiration, but at autopsy no pathological signs are found in the brain tissue which can be associated with the paroxysm. This is quite conceivable if we think of the vascular spasm and its results as seen in the retina, extremities, and intestines. Both irritation and anæmia of the medulla cause slowing of the pulse. Halberton's case, one of the earliest of this kind described and referred to by all writers on the subject, was that of a man who developed the symptoms three years after a fall from his horse in which he struck on his head. The autopsy revealed narrowing and deformity of the foramen magnum, and thickening of the dura mater which was sufficient to compress the cervical cord and medulla. Other cases of Stokes-Adams syndrome have been observed which have come to autopsy and very skilled pathologists were unable to demonstrate any lesion in the medulla or in the cardiovascular system.

The whole symptom complex may arise from irritation of the vagus trunk. Stackler[1] reports one such case which, however, is not satisfactory in its pathological results and he cites a number of others from literature. Probably the best evidence of such symptoms arising from pure vagus irritation is to be found in Tanhoffer's[2] description of his experience with a pupil who was making some experiments on his own vagi for his professor's benefit. This student compressed with his left index finger and left thumb respectively his right and left vagi. Tanhoffer observed, while making sphygmographic tracings of the pulse, that his pupil did not respond to a question. On looking at his face, Tanhoffer observed his eyes had a glassy stare, and the left arm was rigidly contracted, with the finger and thumb pressing at the throat. The student had lost consciousness. Tanhoffer pulled the hand away from his throat and observed the pulse had ceased, the sphygmogram showing no tracing of the pulse for 67 seconds; then the pulse steadily rose in frequency. The student was unconscious for several minutes, and when consciousness

[1] *Revue de méd.*, vol. ii, p. 404.
[2] *Centralblatt f. med. Wissenschaft*, 1875, p. 403.

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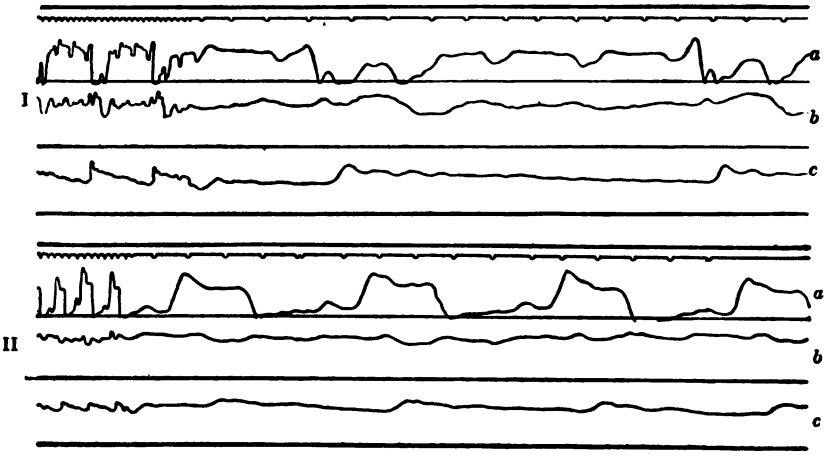
returned he was dizzy and nauseated. Even the following morning after a good sleep he suffered from dizziness, loss of appetite, coated tongue, and slight nausea. Here we have all the phenomena which may occur in Stokes-Adams syndrome occurring in a healthy young man after mechanical irritation of both vagi.

The physical signs over the heart, besides the bradycardia and arhythmia, vary with the manner of heart-block or bradycardia. In instances of heart-block one may count the pulsations in the external jugular vein, as the veins of the neck under such conditions are greatly dilated. Under such conditions there can be seen two or more distinct pulsations in the veins for every pulsation in the artery. When the tricuspid valve is sound the venous pulses are due to the contraction of the auricle and can be seen to precede the carotid pulse in a complete cardiac cycle, and when the block at the auriculo-ventricular bridge occurs a pulse is visible in the jugular vein which marks the systole of the auricle.

FIG. 26



I. Stokes-Adams syndrome. Tracings from *a*, heart; *b*, jugular vein; *c*, radial artery. II. Tracings from the same patient two months later when the pulse rate was 60 per minute. The time marking is in fifths of seconds.

The ventricles manifest some signs during the blocked systole. Although no pulsation occurs, one may hear a very faint sound over the ventricles. This is probably due to the closure of the atrio-ventricular valves which marks the termination of the auricular systole. At other cycles there may be an impulse over the ventricle due to an extrasystole which originates from the bridge and is not sufficient to produce a pulse, or, as Huchard suggests, such pulsations are due to distention of the ventricles from the auricular wave. This point can be determined only by an analysis of the comparative tracings of the venous and arterial pulses and cardiac impulses.

The tracing was taken from a man, aged thirty-seven years, who had typical Stokes-Adams syndrome, bradycardia varying from 20 to 30 per minute, fainting, convulsions, and slumber apnœa. There was marked arterial sclerosis. The tracing of the precordial impulse was procured by means of a two-inch funnel placed over the apex, the venous pulse by means

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of a smaller funnel applied over the jugular vein, which was large and pulsating rapidly. All of the points in this instance could be detected by physical examination independently of the polysphygmograph. The venous tracings reveal, in each cardiac cycle, three pulsations of about equal size followed by a fourth shorter pulsation, which is evidently transmitted to the ventricle, as evidenced by the radial tracing below and the carotid tracing which is interjected after the fourth venous pulsation from the underlying artery. There are then four contractions of the auricle to one of the ventricle. The precordial tracings show four impulses synchronous in time and similar in form to the venous pulses.

Following the short impulse, which occurs with the short auricular wave which is transmitted to the ventricle, there is a sharp decline in the apex tracing, which suggests the systolic apex retraction in synechia cordis. This is, however, not the case. In place of a retraction the impulse was plainly palpable at this instant. The volume of the ventricle increases in volume with each untransmitted auricular systole and lies in contact with a large area of the anterior thoracic wall. The recession from the thoracic wall which accompanies a complete systole after such a hyperdiastole accounts for the rarefaction under the funnel covering the apex, though at this same instant an impulse was clearly palpable over the apex of the heart. One could hear a faint sound accompanying each one of the three untransmitted auricular systoles. This sound was probably produced by the closure of the atrio-ventricular valves at the end of each auricular systole. That the systolic retraction over the apex was due to the recession of the hyperdiastolic ventricle can be proven by the systolic impulse revealed in the tracings taken several weeks later, when there was a heart rate of 60 per minute. This change was apparently wrought by a vigorous antisyphilitic therapy with both mercurials and iodide of potash. After this improvement, the heart rate remained at 60 to 70 per minute unless the patient exercised; then the heart rate became slow as before. The patient said, "The more I exercise, the slower my heart goes." The fainting, clonic convulsions, recovery from heart-block under antisyphilitic treatment, and subsequent slowing of the heart rate with exercise, all lure us to the ready conclusion that the heart-block was due to syphilitic disease of the bundle of His. But there were other features which serve to throw doubt on this explanation. The patient had sclerosis in all the accessible arterial distributions. During five consecutive months in which heart-block persisted, the patient dared not fall into a deep sleep. Whenever he went soundly to sleep automatic respiration ceased. If he was permitted to lie in this state of apnœa until he awakened spontaneously, he awoke with air hunger which was very distressing. The heart rate was not in any way implicated in this procedure.

During the greater part of the night the nurse awakened him promptly when respiration ceased. This procedure prevented the patient getting any sleep until the early morning hours, when he would finally fall into a light sleep which did not interfere with automatic respiration. After this prolonged siege with heart-block and slumber apnœa which lasted five months, his pulse was observed one morning to have attained a rhythmic and regular rate of 60 per minute. From that time on he could sleep soundly through the night without any respiratory disturbance. The manner of recovery here does not offer conclusive proof that the slumber apnœa and heart-block were both due to bulbar disease from sclerosis of the basilar

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arteries, but we know a definite relation exists between slumber apnœa and sclerosis of the cerebral arteries and we know of no causal relation between bradycardia and slumber apnœa. Such a case suggests the need of careful histological studies of the bulbar nuclei in cases of Stokes-Adams syndrome.

Disease of the bundle of His no doubt explains some cases of heart-block, but it is improbable that it will explain all cases any more than myocardial disease will explain all other changes in rate and rhythm of the heart-beat. There is another significant fact relative to this point, viz., the bulbar origin of the Stokes-Adams syndrome. Some cases have been reported in which the paroxysms of bradycardia and accompanying brain symptoms could be avoided by inverting the body. If measures which increase the blood supply to the brain will stop the paroxysms of Stokes-Adams disease, it seems reasonable to assume that bulbar anæmia (in some cases at least) causes the heart-block. Clinical experience and laboratory experiment have both shown the causal relation between bulbar anæmia and apnœa.

Prognosis.—This is grave in any case of Stokes-Adams disease, as the causes of the signs imply, though a prognosis for a short duration of life is not invariably justifiable. Four years ago (1904) the writer, with S. J. Webster, saw a man aged seventy years, who had his first attack of convulsions when sixty-three years of age. Subsequently there were two more attacks. When serving as a soldier it was observed that he had a normal heart rate of 40, which rose to 50 under excitement. His health remained good until the attack seven years ago. From that time until three years ago he suffered from dyspnœa and precordial distress. He had then a much enlarged heart, marked arterial sclerosis, and dilated and pulsating jugular veins. The carotid artery showed 36 pulsations to the minute. The jugular vein showed 72 centrifugal pulses to the minute and these were equidistant; so they were not presystolic and systolic pulses, but pulses from two distinct cardiac cycles, one of which was blocked at the atrio-ventricular bridge and the other was transmitted to the ventricle. A few months later Dr. Webster saw the patient and found his precordial area had increased in size, the distress and dyspnœa had increased, and there were three venous pulses for each arterial pulse. In the summer of 1907 the writer visited him to procure some tracings with the polysphygmograph and found him very much better. The venous pulses had entirely disappeared; the area of cardiac dulness had diminished, and the pulse rate was rhythmic, 76 per minute, and the arterial tension was markedly increased.

Treatment.—Besides the treatment of the underlying cause, such as syphilis, arterial sclerosis, and brain affection, the only specific for the symptoms are: to put the head low or invert the body to counteract the anæmia of the brain, which is supposed to be the cause of the symptoms, and to employ atropine to diminish the inhibitory tone of the vagus terminations. Atropine is of service when the bradycardia is not due to heart-block or affections of the myocardium itself. In heart-block, Erlanger[1] has shown that atropine increases the rate of the auricle and not the rate of the ventricle. Dehio has shown the efficacy of atropine in increasing the heart rate when the vagus inhibitory tone is increased and the failure to give relief when bradycardia is due to disease of the myocardium; but his conclusions should not be rigidly adhered to in treatment, because benefit in myocardial cases may be

[1] *Journal of Experimental Medicine*, vol. vii, No 6, and vol. viii, No. 1.

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got by diminishing the normal negative dromotropic influence of the vagus nerve or vagus nucleus.

Syphilis must not be forgotten in treating any case of Stokes-Adams syndrome. Syphilitic myocarditis involving the bundle of His has been proven in several cases at autopsy. Syphilitic arteritis of the cerebral arteries may also be a cause. Not only iodide of potash, but mercury in sufficient doses must be used, for the chronic arteritis of syphilis responds to mercury when it is unaffected by iodide of potash, although the primary infection may have occurred many years before.

DIGESTIVE DISTURBANCES AND THE HEART.

Circulatory disturbances, caused by disorders of digestion, are comparatively frequent. These patients are rarely so ill that they are confined to bed, and relatively few obtain admission to hospital wards. They are too often regarded as hypochondriacs and neurasthenics, with the imputation that autosuggestion is the source of their trouble.

It is very difficult to determine how much the psychic factor shares in their suffering, and how much the patient's fears contribute to the cause of their symptoms. This is not difficult to understand when we consider the character of cerebral reflex cardiac symptoms. The patient who has once suffered a paroxysmal tachycardia is left in constant fear of a recurrence. They become mentally depressed, and this, of course, increases the disturbances of digestion, until finally such a patient lives in constant terror. From these very sources, however, there can be much learned about the nature of cardiovascular disturbances and the nature of nervous influences over the cardiac cycle.

Secondary to defects in the digestive processes we may have very great modifications in the distribution of blood. There is a constant equilibrium maintained between the splanchnic vessels and the vessels to the limbs, head, and surface of the body. To appreciate this fact, one need only to watch the pulse of a patient during the operation of gastro-enterostomy and observe how the splanchnic vessels swell with blood and how the radial pulse fades when there is any traction exerted on the omentum and mesentery. With such experiences in mind, it is not difficult to conceive why many patients with gastro-intestinal dyspepsia and ptosis of the stomach and intestines suffer from cold hands and feet and have a radial pulse of small volume with low pressure. Some people become very chilly after each meal and invariably walk from the dining table to the open fire or radiator. Why disturbances of blood pressure, blood distribution, and heart rhythm are not more frequently seen in diseases of the digestive organs seems strange. A conspicuous feature of these symptoms, however, is their association with digestive diseases of mild type, while ulcer and cancer of the stomach, obstruction of the bowels, peritonitis, ascites, and meteorism are never associated with such cardiovascular symptoms. Explanatory of this disparity has been offered the suggestion that "grave diseases depress the reflex centres, whereas the milder affections are associated with exaltation of the reflexes." This is merely a response, not an answer to the question. To liberate these reflex stimuli to the heart and vasomotor centres it seems necessary for the viscus not merely to suffer distention, traction, or pressure,

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but these forces must be applied at certain points and in certain directions. These points have not been sufficiently investigated from an experimental or clinical standpoint to justify a positive statement.

No doubt the mental status of the patient is often a determining factor in the production of these symptoms. The person who enjoys mental tranquility maintains an inhibitory tone over his bulbar centres which the neurasthenic and hysterical patients have lost, and, as a consequence, the same impulses from the abdominal viscera meet with different responses in the centres of the medulla or spinal cord. There are symptoms from the heart ascribed to digestive disturbances which are more than mere disturbances in cardiac innervation. These symptoms include not only a vasomotor spasm in the pulmonary arterial branches, but also a passive dilatation of the right ventricle with stasis in the venous system which may lead to œdema of the extremities. This clinical interpretation is found among French writers on the subject, but it is an opinion shared by many of the most eminent clinicians of France. They describe many cases of myocardial insufficiency in which the incompetency is confined to the right ventricle. The point of resistance is located in the pulmonary arteries. Some animal experiments have been described in support of the theory, but so far they have not been at all convincing. If the French interpretation of the subject is correct, medical men elsewhere have a too mechanical view of circulatory disturbances.

A patient is described as having a rapid pulse of small volume with accentuated second pulmonic sound and palpable diastolic impact over the pulmonic area. The right heart is dilated with gallop rhythm confined to the right ventricle; the liver is slightly enlarged and sensitive to slight pressure. In severe cases the patient may have dyspnœa, cyanosis, and œdema. These patients are kept in bed, put on a slender diet, and given mercurials and saline cathartics in moderate doses, and with relief of the splanchnic vessels the cardiac symptoms disappear. Cases of pure gastric disturbance due to hyperchlorhydria have been described with this train of symptoms and appropriate treatment of the gastric disorder was followed with relief of the heart symptoms.

Such signs of myocardial incompetency relieved by the treatment described are not uncommon in any hospital ward, but the interpretation of cause and effect is the reverse of that described. We regard the hepatic and gastro-intestinal symptoms as secondary to the myocardial incompetency and the relief afforded by the treatment as due to lowering the arterial resistance in the splanchnic vessels and the relief to the myocardium from rest in bed. This is a subject which requires further investigation. Traction on the mesentery may produce great vascular relaxation in the splanchnic vessels as above described in operative procedures, as seen in a young woman with a femoral hernia who would faint whenever the bowel escaped through the femoral ring. Traction on the mesenteric attachments apparently causes intermissions in the heart beat as well as an impaired blood supply to the head and extremities. Patients with lax abdominal walls and ptosis of the viscera sometimes experience relief from cardiac intermissions and improve their mental state by applying a good abdominal supporter. A most unequivocal experiment on distention of the stomach with its results to the cardiac rhythm was performed unwittingly while attempting to learn the relation of an epigastric tumor to the stomach. For this purpose the patient

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was given the usual amount of bicarbonate of soda and tartaric acid to inflate the stomach. It was later learned that the palpable epigastric tumor was only a part of a carcinomatous growth which involved the whole stomach and had transformed it into an unyielding, rigid sac. The patient sat on the edge of the bed during the procedure, and directly the second draught was swallowed he showed signs of great distress. He became livid; the jugular veins were enormously distended and pulsated rapidly. The arterial pulse was very slow and arhythmic, although full and of fair pressure when it did occur. There was not sufficient time to determine the rate of the pulse with accuracy, for the whole procedure could not have lasted more than half a minute. The rate, however, was estimated at the time as being less than 20 per minute. With the eructation of gas from the stomach the normal color returned to the face; the jugular veins collapsed and the heart became rhythmic, with a rate of 80 per minute. Whether this patient had a genuine bradycardia or heart-block is not perfectly clear, although the marked distention of the jugular vein and the slow arhythmic arterial pulse of full volume are evidences of heart-block. The symptoms, so far as the heart was concerned, were identical with those in Stokes-Adams syndrome.

It is a common experience to see extrasystole or tachycardia accompany gastric distention, but in the experiment just described an intragastric pressure was reached which is never seen in the natural course of a dyspeptic attack. Under essential paroxysmal tachycardia an instance of transmission from tachycardia to bradycardia with heart-block is described. The change from tachycardia to bradycardia was as sudden as the onset of the tachycardia. A comparison of these two cases suggests that the appearance of tachycardia or bradycardia with heart-block will depend on the degree of intragastric pressure which is developed. McKenzie[1] regards tachycardia as a series of extrasystoles in which the rhythm is ventricular and arises from the auriculo-ventricular bridge. If this be true (with the advent of bradycardia and heart-block), the rhythm must originate at the auricle. Constant bradycardia is not extremely rare as a neurosis of the heart in conjunction with digestive disorders, but the cases which have come under personal observation have not been reflex in character as the two above described. The other cases were true bradycardia without arhythmia, and were due either to some toxic condition which originated from the digestive disturbances or were direct symptoms of the psychosis. The latter seems more probable.

During these attacks of reflex tachycardia from distention of the stomach, the stomach does not protrude in the epigastrium. We know that the dome of the cardiac end of the stomach may stand on a level with the third intercostal space in the nipple line and still cause no protrusion in the epigastrium. Clinical evidence tends to show these reflex impulses to the heart are liberated from the cardiac end of the stomach and œsophagus and not from the pyloric end of the stomach. If direct pressure against the under surface of the diaphragm which displaces the heart were sufficient to liberate a series of ventricular extrasystoles by direct irritation of the atrio-ventricular bridge, then meteorism, ascites, and large abdominal tumors should commonly be associated with tachycardia. But, as we have seen, severe distention of the stomach is associated with bradycardia and heart-

[1] *British Medical Journal*, March and April, 1905.

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block and not with tachycardia. Reflex tachycardia from gastric disturbances begins and ends with the same suddenness as attacks of essential paroxysmal tachycardia. Unlike these cases, however, the attacks are not so long in duration, rarely more than two hours. The patients are not cyanotic or dyspnœic. The jugular veins are rarely dilated, and there is rarely any dilatation of the heart. The pulse is always extremely small, so small indeed, with a heart rate of 240, that it is scarcely perceptible in the radial artery. In the appearance of the patient there is nothing but slight pallor to indicate that anything unusual has happened. The tachycardia is commonly ushered in with a few premonitory intermissions and the attacks often terminate in two or three slow beats before the normal rate is established. Sometimes the tachycardia begins directly, without the slightest warning, in the form of several irregular beats.

Patients who suffer from reflex tachycardia are constipated and generally suffer from insomnia. The common sequence of events is first the constipation, then insomnia, which after a few days is followed with an attack of tachycardia. The use of alcohol, tobacco, tea, and coffee are undoubtedly contributory factors in many cases. One patient, a woman aged forty years, whose first attack of tachycardia occurred in her eighteenth year, developed an arhythmia on one occasion which clearly originated from the œsophagus and cardiac end of the stomach. She had sour eructations from the stomach for several days, and one evening she noticed that every time she swallowed the heart would intermit. This reflex inhibitory influence on the heart originated through centripetal stimuli from the superior laryngeal and œsophageal branches of the inferior laryngeal. The vagus centres were in an abnormally irritable state to respond in this manner to stimuli which ordinarily have no effect on the inhibitory vagus centres. She was unable to eat or drink anything that evening, and went to bed with her head turned to one side and a towel tucked under the corner of her mouth to catch the saliva. Every time she swallowed the collected saliva her heart would intermit. The symptom lasted until the following morning. Gastric lavage was then performed and the tube was swallowed without causing any intermission in the heart beat. The patient lay on the right side during this procedure, and when she turned on her back or to the left side while there was a pint of water in the stomach the heart would intermit. There has been no recurrence of this symptom for the past year.

There is no association between any qualitative or quantitative disturbance in the gastric secretion and these attacks of tachycardia so far as could be ascertained in the cases under observation. If the patients have free passages from the bowel, have restful sleep at nights, and are not tired by any undue physical or mental work or emotional excitement, they are quite free of their trouble.

The effect of distention of the stomach from gas or food is well recognized in the course of diseases of the myocardium, the heart valves, and the aorta. It is not uncommon to find acute dilatation of the heart in old myocardial and valvular lesions which is caused by constipation and meteorism. So, also, is cardiac pain in disease of the aorta directly dependent on the ingestion of a very moderate amount of food, when the increased work put on the heart by the demands of digestion could not possibly be the source of the pain. The routine practice, in treatment of acute myocardial incompetence in chronic diseases of the heart muscle and valves, is rest in bed and saline

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cathartics, postponing the use of digitalis until it is known whether the salines may give the desired relief. Lowering the blood pressure is not the only source of relief from the use of cathartics. The cardiac patient complains of anorexia, palpitation, arhythmia or cardiac pain when compensation is well maintained, so that the digestive trouble cannot be accounted for by stasis. Diminution in the area of dulness of an enlarged heart is mentioned by Fraentzel[1] as commonly following relief from constipation. The same writer mentions the precautions taken at health resorts where springs of carbonated water are visited by patients. Patients with cardiac diseases are cautioned against drinking water highly charged with carbonic acid, because early in the history of these springs many cases of sudden death occurred when the patients drank freely of carbonated water.

All patients with heart disease find they are much freer from discomfort when they put only a small bulk of either solids or liquids in their stomachs and have free movements from the bowel. But the margin of tolerance in these patients is so small, even when the heart is in a fairly good state of compensation, that it does not seem reasonable to explain the pain, arhythmia, dilatation, and even sudden death by added work to the heart from increased resistance in the splanchnic vessels. Reflex nervous effects on these diseased hearts from the digestive tract are no more mysterious in their mode of production than the proposed mechanical method of production which is the more popular conception of this common clinical symptom. It is not unreasonable to believe that a diseased heart will alter its manner of response to reflex stimuli so that a stimulus (which under normal conditions would not affect the rhythm) may in a diseased heart elicit reactions quite different from the one we see in a healthy heart. There does not seem to be any evidence which shows that the prolonged and oft-recurring attacks of tachycardia due to reflex causes from the stomach will cause organic disease of the heart, nor does this association of symptoms between the stomach and heart imply any acquired or congenital defect. These symptoms occur in persons over such a long term of years, with such a sound circulatory system in the interims between the attacks, that we are compelled to believe the fault lies in the centres rather than in the character of the gastric disturbance or in any cardiac defect. The arhythmia and tachycardia in such patients are known to occur often as the result of nervous exhaustion or great emotional excitement. Another proof of the psychical factor in the production of these phenomena is the great improvement which attends the conviction on the part of the patient that the trouble is really due to reflex causes and not to any disease of the heart. If these patients learn they can arrest the tachycardia by any procedure, they gain confidence in themselves and the attacks grow less severe and less frequent.

Nothnagel's conception was that there existed a close analogy between paroxysmal attacks of tachycardia and epilepsy, particularly petit mal, and this is probably in the direction of a solution of the problem. In the case of the heart there was a temporary suspension of inhibition with an abrupt beginning and termination. But here we meet the problem of determining where the suspension of inhibition takes place. In the central nervous system or in the heart? During recent years, champions of the myogenic theory of cardiac autonomy have dominated the field so that there seemed little hope left

[1] *Idiopathische Herz Vergrösserungen*, Berlin, 1892.

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for the proof of regulatory centres in the heart. During the past two years there has been some valuable evidence in support of the neurogenic theory with which students of the subject must reckon. Bethe[1] has shown the existence of a rich supply of nerve fibers and ganglion cells in the entire heart muscle of the frog, even fibers and ganglion cells in the apex of the heart. Carlson[2] has offered the best evidence thus far presented on the neurogenic side of the question. One must be cautious in applying the results of physiological experiments on low forms of animal life to the human heart, but Carlson's work shows that much of the support to the myogenic theory from observations on lower forms of animal life have not been correct. He furthermore has shown the dependence of the heart of the limulus on its nerve ganglia for both its autonomy and coördinated contraction of various portions of the heart. Inhibitory influences on the limulus heart from ganglia of the abdominal cord are exercised through the medium of the heart ganglia and not directly on the heart muscle. If one applies the results of the work of Bethe and Carlson to the human heart, the evidence is very strong that cardiac autonomy and coördination are dependent on the intracardiac nerve centres and fibers. The heart stimulus is constant, but rhythmically interrupted. This rhythmic interruption or inhibitory influence persists in the after-living human heart, which recovers its rhythmic contractions many hours after removal from the body when the coronary arteries are irrigated with an appropriate serum. In the light of this experiment it is not at all to be wondered at that tachycardia cannot be produced by any experiments on the extracardial nerves.

The inhibitory centre lies within the cardiac ganglia and to produce the "cardiac epilepsy or petit mal" which Nothnagel terms tachycardia, the suspension of inhibitory influences may take place in the intracardiac ganglia and not in the bulbar ganglia cells. Stimulation of the accelerator nerves and section of the inhibitory nerves fail to produce tachycardia. Tachycardia may be produced by continued stimulation of the atrioventricular bridge, so that the attempt to arrive at a solution by exclusion is blocked by the question whether tachycardia is due to stimuli which pass through undiscovered paths to the accelerator fibers or to suspension of the intracardiac inhibition. If reflex tachycardia is due to a suspension of inhibitory influences, it seems evident that this must be accomplished through influences on the intracardiac nervous structures which are now found at least in some animals in great abundance where they were formerly believed to be absent.

Tachycardia from reflex gastric disturbances may often be checked by a hypodermic injection of morphine, but essential paroxysmal tachycardia from myocardial disease is unaffected by morphine. This has been the writer's experience, and, so far as can be determined from the literature, is the general experience. This method is not justifiable in the treatment of reflex tachycardia, because neurotic patients (with whom we have to deal) are too easily taught to resort to their morphia injection.

In reflex tachycardia the most efficient treatment is to induce eructations of gas by giving Hoffman's anodyne in 0.5 dram (2 cc.) doses with sugar or water, or by giving bicarbonate of soda (a teaspoonful dissolved in a

[1] *Allgem. Phys. u. Path. des Nervensystems*, Leipsic, 1903.
[2] *American Journal of Physiology*, 1904 and 1905

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half-glass of water). In some attacks there is no apparent association between the accumulation of gas in the stomach and the tachycardia. Cessation of tachycardia is not marked by escape of gas through the cardiac orifice or through the pylorus. Compression of the abdomen by drawing on the ends of a broad towel wrapped about the abdomen or inverting the body, thus emptying the splanchnic vessels and at the same time stimulating the medullary vagus centres, are the best methods of arresting the attacks, because such methods convince the patient of the purely reflex character. When this is once thoroughly impressed on the patient's mind, much is won toward preventing a recurrence of the attacks, and should they recur the patient is not thrown into a panic from fear of sudden death. A tranquil mental state assists in combating the individual attacks and aids much toward warding off a return of the symptom.

Although bradycardia can be produced experimentally by distending the stomach of an animal, and was produced in the human subject in the manner above described, it is not the usual form of reflex neurosis of the heart commonly seen. In neurasthenia and hysteria, bradycardia is seen in conjunction with nervous dyspeptic symptoms, and is usually accompanied by anæsthesia of the larynx and pharynx, narrowing of the visual field, and regional anæsthesia of the skin. In von Noorden's cases the heart rate could be still further reduced by suggestion. Paroxysmal bradycardia associated with disturbances of gastric digestion is of longer duration than tachycardia from the same source. In an instance in a young woman, aged twenty-four years, the attacks lasted as long as two days, but during this time there was rarely any irregularity. The pulse rate was 50 per minute and the character of the pulse and heart impulse was a perfect reproduction of the pulse and precordial impulse which accompany vagus irritation. This patient had her attacks several times in a year after the fourteenth year and called them "attacks of palpitation." While the bradycardia lasted she went about her usual occupations and complained only of the uncomfortable throbbing over the heart and in the carotid arteries. The gastric disturbances in these attacks were manifested by sour eructations, although there was not a great amount of gas in the stomach or the bowel. Bicarbonate of soda gave some relief, but there was not a prompt return to the usual heart rate of 76 per minute after the eructation of gas, as usually occurs in attacks of tachycardia.

The act of vomiting in children causes slowing of the heart rate and cardiac intermissions, signs which may arouse suspicion of beginning tuberculous meningitis. In such cases the cardiac inhibition originates from the œsophagus and the region supplied by the superior laryngeal. Depressor irritation from the superior laryngeal is a phenomenon with which we are perfectly familiar, from many clinical experiences and experimental confirmation.

In paroxysmal bradycardia of reflex origin or constant bradycardia of nervous origin, atropine in sufficient amounts to reduce the vagus inhibitory tone will relieve the symptom, but will not protect the patient against subsequent attacks.

SEXUAL ORGANS AND THE HEART.

The pelvic organs and external genitalia have a rich sympathetic nerve supply from the inferior hypogastric plexus, which is a continuation of

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the solar and aortic plexuses. There is also a direct connection between the renal plexus and the ovaries. Vasomotor depression and accelerator impulses to the heart are very common manifestations associated with irritation of the pelvic organs in both male and female. Vasomotor disturbances and increase in the heart rate are very much more common than inhibitory influences and intermission in the heart rhythm.

Paroxysmal vasomotor depression follows the act of coitus in some men so they are compelled to keep in a horizontal position for several minutes until the vasomotor tone recovers. Elderly men who marry young women are commonly known to develop myocardial insufficiency. Many instances of death from angina pectoris during coitus are known to occur in persons who have disease of the valves or coronary arteries and myocardium.

There is great difficulty in learning all the factors which are responsible for exhaustion and cardiac symptoms in cases where excessive coitus is supposed to be the underlying cause. This is almost invariably combined with abuse of tobacco and alcohol, insufficient sleep, and gluttony. It is the combination of all these indulgences which serve to weaken a normal heart or cause dilatation of a diseased one. Fraentzel refers to several students who spent a few weeks in riotous living of this sort. At the end of a debauch both young men had clearly demonstrable enlargement of the precordial area of dulness and other signs of myocardial impairment. It would not be correct to ascribe all the symptoms to venereal excess when gluttony in eating and excessive drinking and smoking are also implicated. Myocardial disease is commonly seen in persons who have led intemperate lives. Of all the forms of sensuous indulgencies, the one oftenest enjoyed to the exclusion of all other excesses is gluttony, and, therefore, the one form which we most frequently see as the sole etiological factor of myocard al disease.

In some of these patients vigorous exercise increases the palpitation and heart rate to such a marked degree that the limitations in exercise permitted nothing more vigorous than walking at a moderate gait. Although the observations in certain patients tend to prove the sexual origin of the cardiac symptoms, we must use great precaution in arriving at such an opinion by exclusion of all other factors. Enlarged mediastinal glands which were not demonstrable, or the results of a former infection which may have been forgotten in the personal history, could produce such cardiac symptoms.

Cardiac palpitation with rapid pulse and slightly increased cardiac volume are described as results of excessive masturbation. Probably the cerebral cortex in such cases is as much the source of these symptoms as the sexual organs. Any factor which is so productive of painful mental experiences and introspection cannot be clearly differentiated as the sole cause of disturbances in the rate and rhythm of the heart. Another source of error in observations of this kind has been the interpretation of a slight increase in the volume of the heart. In the past there has not been sufficient caution exercised in differentiating between active and passive cardiac dilatation. The former kind of dilatation does not imply a myocardial defect and may result from disturbance of cardiac innervation, when the myocardium is sound.

Kisch[1] describes (in a monograph devoted to the subject) two instances

[1] *Uterus und Herz in ihren Wechselbeziehungen*, 1898.

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of vaginismus in married women, in which every attempt at coitus was followed by severe palpitation and tachycardia which lasted for half an hour. The pulse is described as pulsus celer with dicrotism. In one case the woman had been married for fifteen years and never had successful coitus, the hymen, which was unruptured, was treated with cocaine and stretched. In four weeks after this she was able to have coitus without pain or tachycardia and in ten months gave birth to a child. He also refers to several instances of sudden death due to minor operations on the external female genitalia which were believed to have resulted from reflex stimulation of the bulbar cardiac centre. Increase of the pulse rate and arterial pressure and slowing of the heart rate and arrest of the heart beat have all been observed as effects of traction on the ovaries.

Pallor, low blood pressure, rapid heart rate, and vomiting are well-known symptoms of injuries to the testicles. Two young women, both multiparæ, neither of whom had any disease of the uterine adnexæ nor malposition of the uterus, complained of faintness after defecation. One patient was compelled to lie down for a few minutes on the bathroom floor, after a large stool, to keep from fainting. Both these patients were tall and very long-waisted, with lax abdominal walls and ptosis of both kidneys, liver, and stomach. Although the perineal support to the uterus was sufficient to retain the uterus in a normal position, the whole perineal body was abnormally flexible and pouched downward much more than normally when the patient pressed as at stool. Excessive mobility of the floor of the pelvis was responsible for traction on the pelvic structures during the act of defecation, and this produced, through irritation of the abdominal sympathetic, a transient vascular relaxation in the splanchnic vessels. Symptoms quite like those of exophthalmic goitre have been observed during the menstrual period, which ceased during the interim. H. Cohn (cited by Kisch) described one case in a young woman who had cardiac palpitation, swelling of the thyroid gland, and exophthalmos at the menstrual period. All these symptoms ceased with the end of the menstrual period. There are many cases of disturbed cardiac function which are described as cured by some gynæcological treatment, but it is very difficult in many such cases to know if the heart symptoms are the direct result of reflex nervous disturbances or consequent on the neurasthenia which so often accompanies affections of the generative organs.

The beginning and end of menstruation are often associated with palpitation, rapid heart, and sudden vasomotor oscillations. The symptoms appear in girls often as they commence to menstruate and cease after the menstrual periods are established. Hot flushes, palpitation, and rapid heart are symptoms most women expect at the menopause. The female insane commonly have exacerbations of cerebral symptoms at the menstrual period. Instances of paroxysmal tachycardia with a heart rate of 200 have been known to develop at a time when the menstrual flow failed to appear at the proper time and the normal heart rate returned with the menstrual flow. Such cases need to be observed for a long period before a final opinion can be formed. The career of an essential paroxysmal tachycardia may begin coincidently with such an experience, and only prolonged observation of such a case would show the real significance of the tachycardia, for many of these patients go a year and more without a recurrence of the attacks.

Coitus reservatus is credited with causing disturbances of the heart

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rhythm and rate, but it is doubtful if this departure from the normal can in itself have any more injurious effect on the heart than other deviations from sexual rectitude.

There are many sources of error in interpreting the physiological relations between diseases of the sexual organs and reflex symptoms in the heart and vasomotor system, and though their exact physiological relations have not yet been clearly shown, it is a factor which must never be neglected in seeking an explanation for disturbances of the heart's innervation in both men and women.

IRRITABLE AND WEAKENED HEART.

Up to the present time there exists no absolute pathological and clinical proof of acute passive dilatation and death from excessive muscular exercise; although there are excellent physiological and clinical reasons for believing they occur, there always lurks the suspicion of other contributory factors in such cases, viz., a remnant of a former infection, congenital defects, or manner of living. So there has not yet been shown a completely satisfactory case with acute changes in the myocardium due to overwork. Opportunities to examine such cases are very rare; so it is not difficult to understand why so few are described. Senac (cited by Krehl[1]) describes the heart of a hunted deer as very flaccid. Düms[2] uses the same term in describing the heart of a soldier who dropped dead on arriving in barracks after a long and hurried walk over difficult ground in order that he might not arrive in quarters too late. Although there exists no doubt of the ability of a man to work a heart which is impaired to death, there is some doubt about a sound heart being worked to death. This is a purely relative matter between the endurance of the skeletal muscles and the endurance of the myocardium. An athlete starts on a mile run; during the first quarter his heart beats more violently and his dyspnœa distresses him more than in the second quarter. He has caught his second wind. This experience is due to the intervention of depressor-nerve stimuli which introduce vagus influences for the conservation of the heart and vasomotor relaxation to lighten the vascular resistance. It is probably this vagus influence which causes the compensatory active dilatation in muscular exercise which has often been falsely interpreted as a passive dilatation and sign of the heart failing under the increased demand of physical exertion.

The vagus is the diastolic and anabolic nerve of the heart, and both influences are conservation measures under such circumstances. The heart is capable of greatly increasing its capacity without causing passive dilatation, and the anabolic effect of vagus influences affects the metabolism of the heart muscle in a favorable manner. The accelerator nerves are the katabolic nerves of the heart. In paroxysmal tachycardia the heart really diminishes in size early in an attack. If the attack is prolonged for several days we then see signs of passive dilatation appear. The heart increases in size and cyanosis, dyspnœa, pulmonary œdema, hepatic stasis, albuminuria, and œdema of the legs develop. These signs have been observed to reach a point

[1] *Erkrankungen des Herzmuskels*, p. 229.
[2] *Handbuch der Militärkrankheiten*, ii, p. 498.

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where it seemed death was imminent, when suddenly the normal rhythm of the heart was restored and all signs of incompetence promptly disappeared. Such a series of events followed by instantaneous recovery would be impossible if the tachycardia were merely a symptom of myocardial disease and not the primary affection. In such a case we are justified in saying the heart exhaustion is due purely to accelerator influences. Experiments show the heart's action depends on the supply of oxygen and the removal of carbon dioxide. Magnus[1] showed that the mammalian heart could be maintained in rhythmic contractions for an hour after removal from the body by simply conducting a current of oxygen through the coronary arteries without any nutrient material. Furthermore, he showed that the contractions could be maintained for a short time if the products of metabolism were carried away by conducting a current of hydrogen through the coronaries. If carbonic acid gas were introduced into the coronary circulation the heart's activity promptly ceased.

The accelerator nerve influences are katabolic in character. If tachycardia alone can produce acute passive dilatation, how much more reasonable is it to believe that such may occur after prolonged and severe muscular exercise, where the blood is loaded with the products of metabolism from the violently acting muscular system and the heart's work is magnified by the enormously increased mass movement of the blood which necessarily accompanies physical exertion. It must be remembered that the increase of the heart's rate from exercise is due to accelerator stimulation, and this is associated with katabolic processes in the heart muscle. The effect on the heart from maximal physical exertion outlasts the effort by several hours. Observations on bicycle riders have shown the heart rate to be still rapid as long as five hours after the exercise. These athletes show more weakened and irritable hearts than any others. This is due partly to the fact that the exercise is adopted by so many persons with widely different physical resistance and the illusory charm about bicycling which makes the rider underestimate the work he is performing. Elie de Cyon[2] suggests that the attitude of the bicycle rider causes compression of the abdomen to such a degree as to overbalance the compensatory vascular relaxation which follows centripetal impulses through the depressor nerves.

The first publications which called the attention of the medical profession to physical exercise as a cause of heart disease were those of Peacock in England in 1865 and Da Costa a few years later in America. Peacock studied the cases of heart disease among the miners of Cornwall who worked in a stooping position in a vitiated atmosphere, and Da Costa studied the functional impairment of the heart (unassociated with any demonstrable lesion of the heart or arteries) which he found in soldiers during the Civil War. Da Costa's[3] cases of "irritable heart" represent a class which, of course, do not come to anatomical examination as a result of the heart affection; so that the real condition of the myocardium in such cases is unknown. From the consideration of the heart's work and its relation to metabolism in the myocardium it does not seem justifiable to regard these symptoms as a neurosis. None of Da Costa's cases were associated with physical exercise

[1] Asher und Spiro, *Ergebnisse der Physiologie*, part iv, p. 771.
[2] *Les Nerfs du Cœur*, Paris, 1905.
[3] *American Journal of the Medical Sciences*, 1875.

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alone. Both the mental and physical hardships of army life were necessarily combined and other contributory factors were also in evidence. Typhoid fever, dysentery, excessive chewing and smoking of tobacco, alcohol, and disturbance of the sexual organs are all mentioned in connection with the hardships of campaigning and camp life. These patients had a continuously rapid heart rate and precordial pain which were much increased with exercise. The physical endurance of these men was not equal to the duties of army life, but after prolonged rest they recovered from their symptoms.

Symptoms.—Precordial pain and rapid heart rate are the two conspicuous symptoms in the irritable heart. The writer has seen these symptoms persist as long as two years in a man, aged forty-five years, who otherwise was in perfect health before the occasion which gave rise to the trouble, and he has continued to enjoy perfect health for several years since the symptoms subsided. This man (to board a train) walked a mile at the top of his speed, wearing a heavy overcoat and carrying a heavy travelling bag in each hand. He was seized with violent pain over the lower end of the sternum and over the heart to the left of the sternum when he arrived in the car. Dyspnœa and cough with expectoration of thin mucus lasted for half an hour. There was slight pain over the heart continuously present, and this was accentuated on very moderate exercise for nearly two years after this experience. The sounds of the heart were normal, but the area of dulness extended one-half inch to the right of the sternum and to the left to the nipple line. The heart rate was never below 80 when he was at rest. Several years later all the symptoms, both subjective and objective, were no longer present. This man had absolutely nothing in his personal history (besides the single, prolonged, and severe effort) which could assist in producing the symptoms.

Such symptoms occur in nervous persons who are subjected to marked vasomotor contractions and who suffer from atonic distention of the stomach and constipation. These persons are not capable of normal physical endurance because of a genuine cardiac impairment, but they are often treated too lightly because of the lack of very pronounced physical signs. Under the head of "irritable" or "weakened" heart are found cardiac disturbances which may have varying etiological factors. Whether the original cause be purely nervous, some infectious disease, intoxicants, or physical exercise, they all have the effect of reducing the heart's capacity for work, and that, after all, is the one essential thing for the physician to recognize. If the symptoms have been brought on by overexertion, prolonged rest, massage, baths, and graduated exercises against resistance should be employed. The character of the diet should be regulated to prevent gastric and intestinal fermentation and constipation. The patient must be cautioned against the danger of overexertion and the use of coffee, tea, alcohol, and tobacco. By observing precautions of this sort, the later development of permanent myocardial disease can be prevented, a probable result if the patient were taught to regard his discomfort as an emanation from his inner consciousness.

Tea and Coffee.—The effect of caffeine on the mammalian heart has been interpreted in as many different ways as there are students of the subject. The most complete study from laboratory experiments is that of Santesson (cited by Heinz).[1] Santesson found that caffeine in moderate doses increased the

[1] *Handbuch der experimentellen Pathologie*, i, part ii, p. 975.

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pulse rate, the arterial blood pressure, and the pulse volume. The increase in the pulse rate is independent of the intracardial nerves and is due to the effect on the seat of the automatic stimulus in the heart itself. The increase of the blood pressure is due to two factors, viz., vasomotor contraction and an increase of the pulse volume, as shown by the pericardial plethysmogram. These findings are quite in accord with clinical experience. In toxic doses caffeine causes arhythmia and ultimately the auricle contracts more frequently than the ventricle.

When coffee is drunk in moderation, it may be responsible for occasional cardiac intermissions, but it is very doubtful if this can be a direct effect. It is more probably a reflex effect on the heart due to disturbances in the stomach digestion. Tea and coffee certainly favor the production of paroxysmal tachycardia in patients who have such attacks secondarily to gaseous distention of the stomach.

Stokes[1] describes three instances (one of which he personally observed) in which paroxysmal tachycardia was ascribed to excessive tea drinking. The writer has seen one such case, but the tachycardia was produced by the unfavorable effects of tea on the stomach digestion; so in reality the tachycardia originated only indirectly from the effects of tea. One woman, aged forty-five years, showed very pronounced physical signs in the heart and arteries which subsided in a few months after abstinence from coffee. This patient complained of extreme nervousness and had what she called "fainting attacks," but from her own description she never lost consciousness. The attacks commenced with a feeling of great exhaustion, violent heart palpitation, and the feeling as though a ball rose up in her throat and caused distressing choking sensations. The heart was enlarged downward and outward to the left. The sharply defined and heaving apex impulse was palpable in the sixth intercostal space one inch external to the nipple line. The heart was not enlarged to the right. The aortic valve closure was palpable in the second interspace to the right of the sternum and the aortic sound was accentuated. Otherwise there were no abnormal signs over the heart. The arterial pressure was high and the katacrotus was of long duration. At the bend of the elbow the prolonged systole of the brachial artery was plainly visible. The urine and the retina showed no signs of nephritis. It was then learned the patient had been in the habit for many years of drinking as much as ten cups of coffee daily. Nitroglycerin was given in doses of $\frac{1}{100}$ grain four times daily for a few weeks, and the patient was instructed to abstain from drinking tea and coffee. The heart rate was reduced from 90 to 76 per minute and all evidences of increased arterial resistance disappeared. There were no signs of thickening in any of the accessible arteries. Three months later the heart's apex was in the fifth interspace slightly internal to the nipple line. This seemed a perfectly clear case of cardiac hypertrophy due to excessive coffee drinking, for directly the coffee was discontinued all signs of heightened arterial pressure, cardiac hypertrophy, and the nervous symptoms disappeared.

Another instance of excessive coffee drinking associated with marked disturbances of the heart's volume and rhythm occurred in a woman aged forty-eight years, who held a very responsible position which greatly taxed both her physical and nervous strength and entailed much loss of sleep.

[1] *Diseases of the Heart and the Aorta*, p. 517.

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From ten to twelve cups of moderately strong coffee had been her daily quantity for two years. The heart was enlarged both to the left and right. The apex was in the fifth interspace one inch outside the nipple line and the right border was plainly demonstrable by percussion one inch to the right of the sternum. The sounds over the heart were perfectly clear, but the heart was very arhythmic. There was no suggestion of any form of allorhythmia. The rate varied from 90 to 110 per minute. The arterial pressure was not above the normal point and there were no signs of an increased peripheral arterial resistance. There were no signs of pulmonary stasis nor œdema of the pendent parts, but the liver was sensitive and enlarged to about three fingers' breadth below the costal border in the nipple line. Strychnine, strophanthus, and digitalis had not the slightest effect on the rate or rhythm of the heart. After a month's rest in bed with a mixed diet, which was taken in small amounts every three hours during the day and coffee being discontinued, the heart rate became slower and less irregular. The dimensions of the heart diminished, but did not return quite to the normal size. The liver was no longer sensitive and resumed the normal size. The patient adopted a hygienic mode of living and was able to continue her work with little discomfort, although the arhythmia and slight cardiac enlargement were still present a year later.

These patients were rare and extreme instances, but they show how anatomical changes may be produced in a heart from prolonged and excessive coffee drinking. Tea and coffee may cause cardiac symptoms either indirectly through reflex disturbances from gastric dyspepsia or directly by excitation of the vasomotor centre and the myocardium.

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CHAPTER IX.

CONGENITAL CARDIAC DISEASE.

By MAUDE E. ABBOTT, M.D.

Definition.—Congenital cardiac disease may be defined as that condition in which, through arrest of development or disease occurring in intra-uterine life, anomalies in the anatomical structure of the heart or great vessels exist, leading to irregularities in the circulation. It is frequently associated with congenital cyanosis and clubbing of the fingers, and constitutes in extreme cases the *morbus cæruleus* of the older writers.

THE DEVELOPMENT OF THE HEART.

It is impossible to approach this subject intelligently without a certain preliminary knowledge of the development of the mammalian heart. A brief embryological statement referring especially to the development of the septa, the involution of the bulbus cordis and sinus venosus, and the disappearance of the primitive aortic arches, is therefore necessary here.

The mammalian heart, in the rabbit and probably in man, consists originally of two straight tubes placed independently on either side of the body, which merge together as the ventral cleft closes in and finally fuse, the septum thus formed becoming entirely obliterated before the permanent interventricular septum begins to appear. Meanwhile a twisting of the heart upon its long axes occurs, and it becomes no longer symmetrical, but S-shaped, with the ventricular portion bent forward and downward and the auricular part upward and backward. It now consists of two chambers, a single ventricle forming its anterior and lower part *giving off the aortic trunk from its right upper angle*, and a single auricle with its sinus venosus lying behind and to the left (Figs. 27 and 28). At this stage it resembles the four-chambered heart of the fish, and is especially interesting in regard to the formation of the bulbus cordis (*i. e.*, that part of the heart giving off the primitive aorta). The recent researches of Greil[1] on the reptilian heart and of Keith[2] show that the bulbus in the mammalian heart is at first an independent chamber which is taken up in the wall of the ventricle at an early stage.

The auricle next shifts upward, coming to lie above the ventricle, and its auricular appendages develop enormously, pouching forward on either side of the bulbus (Fig. 30). The auricular canal, in which are developing the endocardial cushions which are to separate the two venous ostia, has become elongated and still opens into the common ventricle entirely on the

[1] *Morph. Jahrb.*, 1903, xxxi, p. 123.
[2] *Festschrift of the Quatercentenary of Aberdeen University*, July, 1906.

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left side. The sinus venosus is now a separate cavity opening into the auricle on its right wall posteriorly through a narrow cleft, the edges of which project into the auricle as the valvulæ venosæ dextra et sinistra. At its upper

FIG. 27

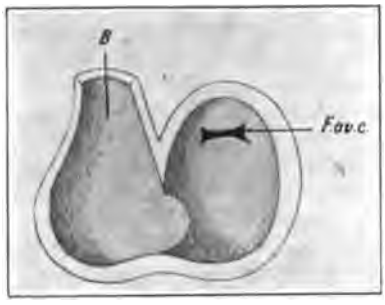


FIG. 28

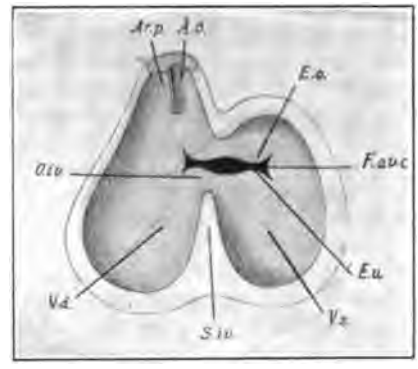
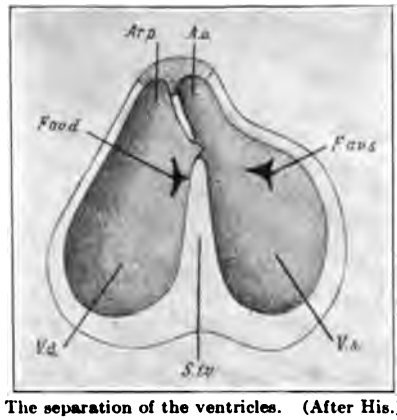


FIG. 29



The separation of the ventricles. (After His.)

FIG. 27.—Embryo 1.9 mm long. The single ventricle gives off the common arterial trunk (*B*) from its *right* upper angle, and receives the common auriculo-ventricular orifice (*F.au.c.*) entirely on its *left* side.

FIG. 28.—Embryo 3.5 mm long. The common trunk has moved somewhat to the left and is divided by the aortic septum. The interventricular septum (*S.iv.*) divides the ventricle into two parts, leaving the interventricular foramen (*O.iv.*) still open above. The auriculo-ventricular orifice (*F.au.c.*) has moved to the right, so that part of it lies in each cavity. *E.o.*, upper endocardial cushion; *E.u.*, lower endocardial cushion; *V.d.*, right ventricle; *V.s.*, left ventricle.

FIG. 29.—The aortic and interventricular septa have united, and completed the division of the ventricles. The pulmonary artery (*Ar.p.*) arises from the right, the aorta (*Ao.*) from the left ventricle, and the right and left auriculo-ventricular ostia (*F.au.d.*, *F.au.s.*) lie in their respective cavities. *V.d.*, right ventricle; *V.s.*, left ventricle; *S.iv.*, interventricular septum. (From Vierordt, Nothnagel's Series, xv, 1-2.)

border it is elongated laterally into the two sinus horns, which receive the two ducts of Cuvier, while a single short trunk, the inferior vena cava, enters it below.

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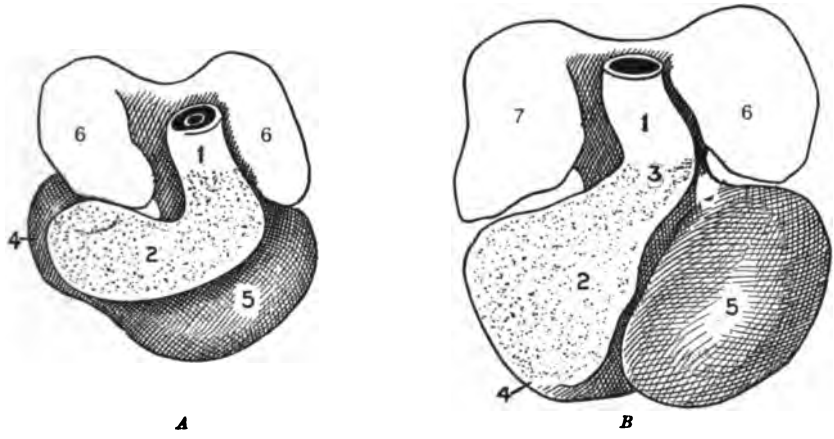
The Interauricular Septum.—The septum between the auricles was described by Lindes in birds and by Rokitansky and His in the human embryo as developing as a single fold, but Born has shown that the division of the auricles takes place through the development of *two different partitions* placed in planes parallel with each other developing successively, parts of both of which are temporary, while parts persist to form the permanent interauricular septum of postnatal life. Of these septa, the one developing earlier, called by Born the *septum primum*, begins about the fourth week from the upper and posterior wall of the auricle and grows forward and downward toward the ventricular cavity, and for some time an opening exists between the auricles at the lower border of this primitive septum known as the *ostium primum*. About the beginning of the fifth week a second opening, called by Born the *ostium secundum*, forms in the

FIG. 30



A *B*

A, heart of a human embryo, 4.5 mm. long. *B*, heart of a human embryo, 5 mm. long. 1, primitive aortic stem from which pulmonary artery and aorta will be developed; 2, bulbus cordis; 3, upper or aortic orifice of bulbus cordis; 4, lower or ventricular orifice of bulbus cordis; 5, ventricle; 6, left auricle; 7, right auricle. (His.) (Reproduced from Malformations of the Bulbus Cordis by Arthur Keith, Quatercentenary of Aberdeen University, 1907.)

upper and back part of the septum primum at the point where this impinges on the posterior and upper wall of the auricle. This second opening grows larger as the ostium primum becomes smaller, and finally disappears entirely (end of fifth week), through the union of the expanded lower margin of the septum primum with the endocardial cushions between the auriculo-ventricular ostia. There thus exists a stage in development when the septum primum is represented by a band of tissue between two orifices, the ostium secundum above, and the ostium primum below.

The *septum secundum* arises considerably later than the septum primum in a plane a little to its right, from the upper wall of the right auricle, and passes downward covering in the upper and anterior portion of the ostium secundum, thus giving it a valvular character, and transforming it into the foramen ovale of fœtal life. A portion of the septum secundum persists in adult life as the *annulus ovalis*, while the *valvula foraminis ovalis* of the

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adult left auricle represents the remains of the primary septum, the primary and secondary ostia of which have both become obliterated.

The Interventricular Septum.—This begins about the fourth week, just after the origin of the auricular septum (Röse), as a low, crescentic ridge on the anterior inferior wall of the ventricle. It grows upward and backward, its posterior and anterior limbs merging with the corresponding walls of the ventricles, while its median curved portion unites with the aortic septum (the aortic orifice having moved over from the right to over-ride the ventricular septum), and with the endocardial cushions of the auriculo-ventricular orifice (which has also come to lie in the median line), so that the ventricles are completely separated from each other and the arterial and venous ostia are placed one in either ventricle (Figs. 28 and 29). The point of union of the aortic with the interventricular septum just below the adjacent ends of the anterior and left posterior aortic cusps remains transparent and devoid of muscle throughout life, and is known as the *pars membranacea*, or undefended space. In some reptiles complete union of the septa at this point never occurs.

The Aortic Septum.—The division of the *truncus arteriosus* begins about the fifth week with the development of two endocardial ridges, lying respectively on its right and left walls, which grow downward and toward each other, coalescing and descending to the base of the heart as a septum which assumes a concave shape and a spiral direction, so that a larger vessel, the aorta, lying to the right and behind, is cut off from a smaller one, the pulmonary artery, lying to the left and in front. According to the theory of Rokitansky, if the position of this septum be altered, so that its concavity face in a different direction, or if it unite with the interventricular septum at an abnormal angle, the relative position of the aorta (which is always the vessel continuous with the fourth embryonic aortic arch) and the pulmonary artery will be changed, or they will be placed in the reversed ventricles and transposition of the great trunks will occur.

The chambers of the heart and the two great arteries have thus been completely separated from each other before the eighth week of fœtal life. Meantime, the right horn of the sinus venosus has been taken up in the wall of the right auricle, and the valvula venosa sinistra has disappeared, a portion of the valvula venosa dextra persisting as the *Eustachian valve*, and the left sinus horn remaining as the coronary sinus, while the left duct of Cuvier becomes obliterated (left superior vena cava). The pulmonary veins form later, opening at first as a single trunk, which is finally taken up in the wall of the left auricle, thereby enlarging it. The semilunar cusps appear to form about the seventh week, from four endocardial cushions, two of which are subdivided in the descent of the septum trunci, so that six cusps, three placed in each artery, result.

The development of the auriculo-ventricular cusps has been specially studied by Gegenbaur and Bernays. The latter divides it into four stages: in the first the valves are simple elevations of the endocardium and have no relation to the myocardium; in the second, connections form between these rudimentary cusps and the muscle of the ventricle, and the inner layers become differentiated to form a part of the heart wall. The chordæ tendineæ are formed later, and the valvular apparatus itself, from being in part muscular, becomes wholly tendinous.

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Primitive Aortic Arches. — According to Boas and Zimmerman (quoted by Vierordt) these number six instead of five, as Rathke described. They are more or less evanescent in all animals, except fishes, in which five persist. In birds and mammals the first, third, and fifth disappear on both sides. In man the fourth left embryonic arch becomes the aorta, the fourth right, the right subclavian, while the left sixth becomes the pulmonary artery.

LITERATURE.

The rarity of cardiac defects, the obscurity of their etiology and symptoms, together with the fact that the cases are so often of serious clinical import, make the subject of congenital cardiac disease of the highest interest. Since the time of Senac[1] it has attracted the interest of many of the ablest workers in the field of cardiac pathology. There are important special contributions from nearly all the earlier writers upon the heart, including Morgagni,[2] Wm. Hunter,[3] Meckel,[4] Louis,[5] Farre,[6] Breschet, Sir James Paget,[7] Gintrac,[8] Chevers,[9] and many others. The first comprehensive study, covering the whole field and reviewing this earlier literature, may be said to be Peacock's,[10] which remains a classic and is still the leading authority in English upon the subject. In Germany the ground has been covered by Lebert-Schrötter,[11] by Rauchfuss,[12] who gives an excellent historical sketch and a full bibliography, and by Vierordt in 1898, in an extensive statistical study of great value. A short account by Thorel[13] brings the subject almost up to date. In French there is the work of Moussons.[14] There is an excellent general account by Humphreys,[15] which should be read by the student.

Perhaps the most valuable and certainly the most brilliant original contribution has been Rokitansky's.[16] This is an analysis of 44 cases of complicated septal defects, together with a study of the normal anatomy of the septa, and of their development as observed by Rokitansky himself, in the human embryo and in the chick. Rokitansky explained all cardiac anomalies associated with septal defects as due to arrest in the development of the cardiac or aortic septa, and to a consequent non-union of the parts. Although the results of his observations have been modified in some important respects, his work is of inestimable value as giving a clue to many

[1] *Traité de la structure du cœur, de son action et de ses maladies*, Paris, 1749.
[2] *De Sedibus et causis Morborum*, 1761.
[3] *Medical Observations and Enquiries*, London, 1784, vol. vi, p. 291.
[4] *De Cordis conditionibus abnormibus, Dissertation*, Halle, 1802.
[5] *Mémoires ou recherches anatomico-pathologiques*, Paris, 1826.
[6] *On Malformations of the Human Heart*, London, 1814.
[7] *Edinburgh Medical and Surgical Journal*, 1831, vol. xxxvi, p. 263.
[8] *Recherches sur la maladie bleue*, Paris, 1824.
[9] *London Medical Gazette*, series of articles, 1845 to 1851.
[10] *Malformations of the Human Heart*, 1858 and 1866.
[11] Article in Ziemssen's *Handbuch der spec. Path. et Ther.*, Leipsic, 1879, Band vi.
[12] In Gerhardt's *Handb. d. Kinderkrankheiten*, 1878, iv, part i.
[13] Lubarsch and Ostertag's *Ergebnisse*, I Abth., 1903, p. 585.
[14] *Maladies congénitales du cœur, volume in the Encyclop. Scient. des aide-mémoire*, Paris.
[15] Allbutt's *System of Medicine*, vol vi.
[16] *Defekte der Scheidewande des Herzens*, Vienna, 1875.

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heretofore inexplicable problems, and especially in regard to transposition of the arterial trunks.

Another single study of much value is that of Thérémin.[1] This consists of 106 observations of congenital cardiac disease made by him at the Hôpital des Enfants Trouvés, St. Petersburg. Full measurements are made in each case, and a plate showing the condition is attached to each.

Reference has already been made to the recent work of Keith. Combining with an intimate knowledge of the finer anatomy of the heart and of the structural arrangement of its muscular layers a series of observations upon stenosis of the conus arteriosus of the pulmonary artery, he has advanced the opinion that congenital pulmonary stenosis is nearly always developmental and non-inflammatory in origin, thus taking the same view in another connection, in favor of arrest of development as a cause, as did Rokitansky in regard to septal defects.

The bulk of the literature centres about three burning questions, which may be stated, with the theories promulgated upon them, as follows:

1. What is the cause of the defect? Is it developmental or due to intrauterine disease?

2. The causation of the cyanosis so often present: Is it due to admixture of venous and arterial currents; or to venous congestion; or to delayed aëration of blood; or to still obscurer causes lying perhaps in tissue metabolism and in the composition of the blood itself?

3. In cases in which a defect of the interventricular septum is combined with stenosis of the pulmonary artery, which is the primary lesion? Is the septal defect secondary, due to the rise of pressure in the chamber behind the stenosed orifice before closure of the fœtal passages had occurred, or is it primary, the deflection of the current of blood through the defect leading to hypoplasia of the pulmonary artery through disuse? Or are both conditions the result of a common cause, an arrest or irregularity in the development of the parts?

An analysis has been made of the records of 412 cases of congenital cardiac disease which will serve here as an illustrative basis. Of these, 205 have been drawn from the *Transactions of the Pathological Society of London*,[2] 25 cases from St. Bartholomew's, Guy's, St. Thomas', and the Edinburgh Hospital *Reports*, a few from personal experience, and the remainder from the recent foreign and home literature. English and American records have been consulted so far as possible, as these sources are often overlooked in the previous statistical studies, which are largely Continental.

ETIOLOGY OF CONGENITAL CARDIAC DISEASE.

Cardiac anomalies may be divided according to etiology into two main groups: those due to *arrest of growth* at an early stage, before the different parts of the heart have been entirely formed, and those produced in the more fully developed heart by *fœtal disease*.

Arrest of Growth.—From the earliest times search has been made for the underlying causes of the arrest of development manifest in cardiac

[1] *Etudes sur les affections congénitales du cœur*, Paris, 1895.

[2] The term *Transactions* as used in the text refers to these.

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malformations. Senac (1749) saw in these only "a license of the formative intelligence," but later thinkers soon came to recognize the fixed laws of growth, under which the different abnormalities take form. Long before Darwin, Meckel in 1812 pointed out the resemblance of certain defects to the hearts of those animals, which present in a stationary form the different stages through which the mammalian heart passes in its development, and explained them as reversions to a more primitive type, even classifying cardiac anomalies into simple bitubular, or insect heart (lowest forms), fish heart, reptilian heart, and mammalian heart with open fœtal passages. Although Meckel's theory never gained ground and is not held to-day, his insistence upon arrest of development as the primary cause pointed the way to the anatomical study of the defect, and to the investigation of the development of the heart, in which such rapid advance has been made of late, and which lies at the basis of all our modern attempts at a scientific classification.

In seeking the causes of the defect we may turn first to the study of associated anomalies. Do these occur in such frequency and constancy as to place their combination beyond the range of coincidence? And if so, may the causes leading to malformations elsewhere, such as disease and adhesions of the amnion, maternal disease, hereditary predisposition, etc., be assumed to act upon the fœtal heart?

In Rokitansky's "Defekte der Scheidewände des Herzens," among 24 complicated defects of the septum, all evidently of developmental origin, associated anomalies such as transposition of the viscera, cleft palate, etc., occurred in 8, that is, in one-third of the cases. Among his twenty defects of the interauricular septum there was only once an associated anomaly, an accessory lobulation of the lung. Vierordt, in the 700 cases reviewed by him, found associated anomalies in 80; he concludes that it is impossible to regard their presence as accidental. Among the 412 cases of congenital cardiac disease here studied there are anomalies elsewhere in the body in 50 cases, that is, in 12 per cent.

These figures indicate, as do those of Vierordt on a larger scale, that it is impossible to regard the presence of associated anomalies as a mere coincidence. And if one approaches the subject from the opposite standpoint, and inquires into the percentage of cardiac defects in anomalies elsewhere in the body, a similar relation is observed. Thus, Ewall Luyken,[1] in an analysis of 74 cases of congenital cystic kidneys, finds cardiac defects four times. Keith found among 23 malformed fœtuses and infants showing anencephaly, hydrocephaly, spina bifida, umbilical hernia, atresia ani, cleft palate, harelip, and stricture of the œsophagus, a malformation of the heart in 14.

Ten of these were deformities of the bulbus cordis.

A combination with mental deficiency, or marked alterations in temperament, is not infrequent. Thus dumbness from birth was reported by Crisp in a case of persistent truncus arteriosus, incoördination of the muscles of sucking and deglutition by Pritchard; and Simmons reports Mongolian idiocy in a cyanotic child with a widely patent foramen ovale which gave marked physical signs. Similar cases of mental defect quoted by Vierordt are: 1 from Leuch of dumbness from birth in congenital pulmonary

[1] *Kiel Thesis*, 1903.

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stenosis, 4 of idiocy, and 1 from Guyon of giddiness with hysterical attacks in a shoemaker aged seventeen years.

On the other hand, the subjects of congenital defects may be especially noted as being of good intelligence. This occurs even when cyanosis is marked. Good illustrations are the cases by Peacock, King, and Quain.

Heredity, although not so clear or constant a factor in cardiac defects as in some other anomalies (*e. g.*, polydactylism), certainly bears some part. Vierordt quotes a case from Potocki of a man aged twenty-nine years, with pulmonary stenosis and defect of the septum, whose mother had congenital cardiac disease, and gives a series from Rezek of 8 cases of heart disease, in two instances congenital, in four generations of a family. Again, Rosenthal's[1] and Jost's[2] cases of symmetrical polydactylism as an associated anomaly are significant, when one recalls the well-known heredity that characterizes this defect. Of much interest also is a specimen in the McGill Museum reported by J. McCrae[3] in which transposition of the viscera and atresia of the pulmonary artery were found in the fifteenth child of a forty-six-year-old mother, who was herself of poor intelligence and had a harelip.

A history of anomalies in the ancestry seems, however, much less common than is one of congenital cardiac defect, other anomalies, or mental weakness in members of the same generation, or of lues, tuberculosis, rheumatism, or acquired heart disease in the parents. These facts suggest that congenital cardiac disease is due more frequently to some toxin or other cause lying either in the environment of the embryo or in the parental organism, and lowering or hindering the growing power of the germ, and less often to an *inherited* lack of formative energy.

In this series there is a family history of congenital cardiac disease in members of the same generation in 10 cases, of repeated miscarriages in the mother (suggesting lues) in 3, of acquired syphilis in the parents in 2, of tuberculosis in 3, of acquired heart disease in 3, and of rheumatism in 8 (of which 1 case of tuberculosis and 1 of rheumatism was in the father).

Baneful influences acting on the mother during the early weeks of pregnancy are sometimes cited, as smallpox, typhoid fever, inflammation of the bladder, great trouble or ill-treatment throughout pregnancy in 2, and fright during the early weeks in 3 cases. In one of these last, that of a child with transposition of the arteries and defects of the septum, reported by Lees,[4] the mother was frightened by the drowning of two women with whom she was bathing when she was six weeks pregnant (misquoted by Vierordt as six months).

Blood relationship in the parents has been noted by Eger and Gerhardt, and must be considered as a possible factor.

Fœtal Disease.—Acute endocarditis has been claimed by some thinkers to be a very widely acting cause of congenital cardiac disease, not only in those cases in which in the fully formed heart the traces of its presence are incontestable, but in the earlier cases of arrest of growth, which are explained as due to its action upon the half-developed embryo. This theory first suggested by Kreysig and expounded by Rokitansky, was pushed beyond

[1] *Munich Thesis*, 1898.
[2] *Giessen Dissertation*, 1896 (quoted by Vierordt).
[3] *Journal of Anatomy and Physiology*, 1905, vol. xl, p. 48.
[4] *Transactions Pathological Society*, London, 1880, xxxi, p. 58.

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its limits by H. Meyer and others, to explain all cases of arrest of growth. With the increasing knowledge of development, the trend of modern opinion is to explain the majority of cardiac defects as arrest of growth, dependent upon a variety of causes as enumerated above, and to class with these many cases of pulmonary stenosis and atresia, formerly thought to be inflammatory in origin. There remains a certain proportion due to fœtal endocarditis, but it is impossible to state the exact degree of its influence, and it is therefore safest to divide cardiac defects into two classes, viz., those in which an arrest of development from any cause has taken place, and those which show, by thickening and cicatricial contraction, that they have been produced by fœtal disease after the heart has been fully formed.

The presence of thickening of the endocardium does not prove that a defect is originally due to an inflammatory process, for cardiac defects, giving rise so readily to abnormal currents and to undue strain upon the valves, are particularly liable to be the seat of future disease.

CYANOSIS.

Congenital cyanosis is a bluish discoloration of the skin and mucous membranes, characterizing the more pronounced cases of congenital cardiac disease in which there is serious interference with the circulation. It differs from the cyanosis of the later stages of acquired cardiac lesions in that it may exist for many years without any signs of venous stasis other than clubbing of the extremities. Its constant association with the other evidences of deficient oxygenation—dyspnœa and clubbing—raises it almost to the ranks of a disease entity, and such, under the titles *Cyanopathia* or *Morbus Cœruleus*, it was long believed to be.

Etiology.—The immediate causation has long been the subject of debate. It has been variously ascribed to (*a*) venous stasis, (*b*) admixture of currents, (*c*) deficient aëration, (*d*) dilatation and new formation of capillaries in peripheral parts of the body, or (*e*) changes in the blood itself, the two latter conditions being looked upon chiefly as subordinate factors.

(*a*) The theory of *venous stasis*, first advanced by Morgagni, and supported by Louis, Cruveilhier, Niemeyer, Rokitansky, Grancher, and most ably by Peacock, has been largely accepted. It does not, however, explain the situation completely. It is difficult to understand why a simple venous stasis should lead to cyanosis and yet remain unassociated with the œdema and anasarca accompanying other forms of back pressure. And, on the other hand, the late appearance of the cyanosis in many cases in which, although the defect has been undoubtedly present at birth, cyanosis only supervenes after some months or years on the occurrence of some event temporarily increasing the embarrassment of the circulation, renders it evident that some other factor, in addition to the mechanical difficulties which the lesion itself presents, is, as a rule, needed to bring it about. Variot[1] reports two instances, practically identical, of pulmonary stenosis combined with *rechtslage* of the aorta and defect of the septum, one patient died at five and a half months without any cyanosis, the other at five years, cyanosis with clubbing having been present from birth. He concludes that cyanosis is

[1] *Journ. Clin. et Thér. Inf.*, 1897, p. 383.

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not constant in congenital cardiac disease. Peacock suggests in connection with a similar case, in which cyanosis was absent, that the marked hypertrophy of the right ventricle present was sufficient to overcome the obstruction to the pulmonary circulation.

(*b*) The theory that cyanosis is due to a mingling of venous with arterial blood (wrongly ascribed to Hunter, as Osler points out) was suggested by Meckel, Gintrac, Bouillard, Farre, Paget, and others. This theory was sharply and apparently successfully refuted by many of the ablest authorities, notably Peacock, but has recently been revived by Bard and Curtillet[1] and others, in a somewhat modified form, and since then has received much support, especially among French writers. These authors describe as *cyanose tardive* a cyanosis occurring as a terminal event, often at the end of a long life, in cases of patent foramen ovale, where some embarrassment in the pulmonary circulation causes a raised pressure in the right heart leading to a flow of blood through the foramen, and sometimes to its forced re-opening when it has been closed. They quote the case of a man, aged fifty-four years, with patent foramen, dying of bronchopneumonia, in whom the late cyanosis had, in their opinion, been produced by the rise of pressure in the right heart. Long before this Peacock[2] reported such a case, in a woman aged twenty-four years, with marked spinal curvature and widely patent foramen ovale, in whom marked cyanosis set in for the first time in the last month of life. Illustrations of such terminal cyanosis might be multiplied.

Sebilleau,[3] quoting Marsan, insists that entrance of arterial into venous blood gives rise to no symptoms, and that cyanosis is present only in complex cardiac lesions in which two factors are present, a communication between the two sides of the heart and an obstruction in the course of the pulmonary artery, so that the current of blood, which normally passes from left to right through the defect, will be reversed, and venous blood from the right heart will enter the arterial circulation through the defect.

In this connection Thomas[4] makes the positive assertion that cyanosis cannot occur without admixture of currents. He quotes cases from Bard and Curtillet and others to show that the terminal cyanosis of pulmonary origin, such as occurs in bronchiectasis, is to be explained on this theory, the entrance of venous into arterial blood taking place, however, in the lung itself instead of in the heart. He reports a case of extreme bronchiectasis with destruction of lung tissue, the foramen ovale closed, in a woman, aged sixty years, in whom cyanosis with a polycythæmia of 6,851,000 red cells per c.mm. developed one month before death. During the last few hours of life, as the heart's action became weaker and less blood was sent to the lungs, to be passed through them unaërated, the cyanosis was distinctly lessened. This fact, he argued, pointed to its pulmonary origin.

On the other hand, certain strong arguments can be adduced against the universal application of the admixture theory. The classical illustration is Breschet's case, in which the left subclavian arose from the pulmonary, and yet the left arm was normal, not discolored. Again, in many instances of biloculate or triloculate heart there is a complete absence of cyanosis. Thus,

[1] *Rev. de Méd.*, December, 1889.
[2] *Transactions Pathological Society*, London, 1859, vol. x, p. 108.
[3] *Paris Thesis*, 1895.
[4] *Zeitschr. f. klin. Med.*, 1901, vol. xli, p. 58.

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Young[1] reports a cor biatriatum triloculare, both auricles opening into a common ventricle, from which arose the aorta and pulmonary artery, transposed and separated from each other by an anomalous septum, in a man, aged thirty-six years, who showed no cyanosis until the last three weeks of life. And Peacock quotes an almost identical case in an infant aged eight months, with only a slight blueness of the lips during dyspnœic attacks. Equally striking is a case of persistent truncus arteriosus, in which, although the blood from both ventricles entered the common arterial trunk, cyanosis was absent.

That cyanosis may be present without admixture of currents would seem to be shown (1) by its presence in a limited number of cases of congenital pulmonary stenosis, in which the fœtal passages are all closed; and (2) by the fact that the most marked pictures of cyanosis with clubbing may occur in acquired pulmonary emphysema and in bronchiectasis. But in these latter combinations lies perhaps the key to the situation. Here, venous stasis, admixture of currents, and local alterations in the capillaries seem to meet. In emphysema, as Thomas points out, large areas of lung tissue have been absorbed, and it is easy to imagine that a certain amount of blood may pass from the pulmonary artery direct to the pulmonary veins, without undergoing due oxygenation in the capillaries by the way. In bronchiectasis, again, areas of loss of substance occur, and tortuous dilated capillaries with thickened walls exist, the bloodvessels here presenting a very similar appearance to that described by Carpenter in the lungs of a case of congenital cardiac disease. The organs were loaded with pigment, the capillaries dilated to three times their normal size, crowded with red cells, elongated, tortuous, their walls thickened and rich in young fibrous tissue elements. Must not many red cells have passed through these thickened channels without receiving their due share of oxygen and the blood have been thus returned, still largely venous in character, to the left heart? Viewed in this light, do not venous stasis and admixture of currents become only a distinction in terms between two conditions leading alike to deficient aëration?

(*c*) The theory that a variety of causes, including a mingling of currents and venous stasis, lead to a deficient aëration of the blood, and that this is the essential element in the production of cyanosis, is formulated by Lees,[2] in the report of a case of extreme cyanosis of the head and upper extremities, less marked on the lower part of the body, in an infant aged seven months, in whom a transposed pulmonary artery rode above a defect of the septum and supplied half the descending thoracic aorta through a very large ductus. In this connection an interesting explanation is offered by Eisenmenger[3] of the cyanosis in his case, a man aged thirty years, with cyanosis and clubbing, a defect at the base of the septum, *rechtslage* of the aorta, but no reduction in the size of the pulmonary artery. He suggests that a deflection of blood through a defect in the septum into the pulmonary artery may lead to a cyanosis by deficient aëration, due to a simple retardation of flow brought about in two ways, viz., the increased amount of blood in the pulmonary circulation causes a slowing of the stream and a lowered intake of oxygen, while the reduced volume of blood passing through the aorta into the genera[l]

[1] *Journal of Anatomy and Physiology*, 1907, vol. xli.
[2] *Transactions Pathological Society*, London, 1880, xxxi, p. 58.
[3] *Zeitschr. f. klin. Med.*, 1897, xxxii, Supp. Heft.

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circulation leads also to retarded flow in the systemic capillaries, and to increased de-oxygenation there. A simple slowing of the blood stream might serve also to explain those cases of congenital cardiac disease in which the cyanosis is transient and appears only during paroxysms of crying, dyspnœic attacks, etc., when the pressure in both pulmonary and systemic circulation is temporarily raised.

(*d*) *Changes in the Bloodvessels and Tissues.*—Microscopic examination of the bulbous enlargement of the tips of the extremities shows dilated and newly formed capillaries and increased formation of connective tissue, in some cases the bone itself being enlarged. Similar changes have been noted in the skin elsewhere in the body (Variot and Gampert),[1] and in the internal organs, and Carpenter[2] suggests that the changes thus produced in the lungs may lead to the cyanosis by producing pulmonary obstruction. Certainly a vicious circle is created. In extreme cases of morbus cœruleus, where the skin is almost black, these changes in the tissues are probably always present, together with the evidences of passive congestion in all the organs. But being themselves the result of the deficient aëration, they can be looked upon only as a secondary cause. The absence of œdema may, perhaps, be explained by these alterations in the walls of the capillaries and smaller vessels, which become fibrosed and thickened, and possibly impermeable to the transudation of fluid. And the further question presents itself: Do dilatation and the new formation of capillaries, with productive changes in the peripheral tissues, thus constitute the essential difference between the clinical picture of congenital cyanosis and that of the simple back pressure of acquired cardiac disease? And do these alterations require for their production the sudden entrance of venous blood into the arterial current, either in the heart itself or more indirectly in the altered vessels of the lung? Or may these tissue changes depend upon the slow evolution of a congenital cyanosis in those critical days of the later fœtal stage and early postnatal life, when the formative energies are strong, and ready for an almost embryonic reactionary development? The answers to these questions must be sought in future investigations.

(*e*) *Changes in the Blood Itself.*—Much attention has recently been directed to the part which the blood and the blood-making organs may take in the causation of cyanosis. Cyanotic blood is undoubtedly darker than normal and the individual corpuscles stain more deeply. This has been ascribed in part to the increased amount of CO_2, or to the lack of oxygen, or, again, to the marked increase in the red blood corpuscles that often exists. The latter feature, however, can have no causal relation to the cyanosis, for not only is it not constant in this condition, but a very high blood count is consistent with an entire absence of cyanosis, as is evidenced in the polycythæmia of high altitudes.

The above considerations may be summarized by saying that the dependence of cyanosis, with its attendant phenomena, upon deficient oxygenation is now fairly accepted as a fact; that the circulation is evidently able to accommodate itself to a certain degree of de-oxygenation, whether this be brought about by obstruction in the course of the pulmonary artery, by a general retardation of flow, or by a mingling of venous with arterial blood, but that as soon as deficient hæmatosis reaches a certain limit, oxygenation

[1] *Gaz. des Hôp.*, xiii, p. 315.

[2] *St. Thomas' Hospital Reports*, xviii.

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becomes insufficient for the needs of the body, and cyanosis results. Pulmonary obstruction alone appears capable of producing cyanosis, but it is still a question as to which of the above factors is the essential one, or in what degree they must be combined to bring the circulation to this limit, or what is the amount of venous blood which can circulate without producing symptoms of deficient aëration. That dilated peripheral capillaries, the dark color and increased viscosity of the blood, must, when present, add their part to heighten the degree of discoloration is self-evident; but being themselves secondary, these conditions are not to be looked upon as etiological factors, but rather as concomitant effects of a common cause. Lastly, in complicated cardiac defects probably all the factors enumerated combine to produce the mulberry hue and the respiratory distress of the typical morbus cœruleus.

Symptoms.—The degree of discoloration varies from a slight bluish tinge of the mucous membranes, appearing on exertion or excitement, to a distinctly leaden hue of the whole surface, becoming purple in extreme cases. It usually increases gradually, and in many cases marked at the last; it is absent at birth, appearing after weeks, months, or even years, when some intercurrent event has heightened the embarrassment in the pulmonary circulation.

The subject of advanced congenital cyanosis presents a very striking appearance. The superficial vessels are often dilated, the tongue "geographical," the tips of the fingers, toes, and nose flattened and bulbous, and the respirations heightened to actual dyspnœa. Traces of anasarca and œdema sometimes occur, but form no essential part of the picture, although of course present at the close in those which terminate with failing compensation. The temperature is usually low and there is a tendency to catarrh, severe colds, and coughs on slight provocation. Hemorrhages, especially from the nose, are prone to occur. Where the cyanosis has set in early, the subjects are often stunted mentally as well as physically, although sometimes they are of unusually high intelligence. In females the menstrual function is often tardy in onset, scanty, and irregular.

Dyspnœa may be absent, but is usually a marked feature and frequently culminates in convulsive seizures attended by marked cyanosis. Variot and Sebilleau have described a remarkable form, called by the latter *cyanose congénitale paroxystique*, in which convulsive seizures, attended with dyspnœa and extreme cyanosis, occur in patients at other times quite free from the latter. Out of 9 such cases recorded by them, in 2 a postmortem examination had been made and showed a combined defect of the septum, pulmonary stenosis, and *rechtslage* of the aorta. Syncope is not uncommon, and attacks of angina occur, in which life may be ended abruptly. A common termination in young subjects is by bronchopneumonia. In older patients tuberculosis is frequent.

The attention of writers has long been directed to the fact that cyanotic patients, although so often weakly subjects in whom pulmonary catarrhs and other sequelæ would seem especially likely to be fatal, frequently pass through the acute infections of childhood well, seeming to show unexpected powers of resistance to them. There are 6 cases in the *Transactions* of patients with extreme morbus cœruleus in pulmonary stenosis or atresia, who had survived severe attacks of measles, whooping-cough, or smallpox, dying later from other causes. On the other hand, life may be abruptly terminated at the very onset of a mild attack of an eruptive fever.

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The Polycythæmia of Congenital Cyanosis.—This is now well recognized to be a common characteristic of cyanotic blood. The red cells frequently number 6,000,000 to 7,000,000, the percentage of hæmoglobin is raised, the viscosity of the blood increased, and, according to Malassez and Vaquez,[1] the erythrocytes are also increased in size. Weil describes in detail the findings in two cyanotic children, aged two and four years, in whom the red cells numbered respectively 7,502,000 and 8,540,500. The thymus was persistent in both, in one greatly enlarged, and microscopically the "hæmatopoietic organs and especially the thymus," and also the other tissues examined, were crowded with vasoformative cells and embryonic capillaries, the whole presenting an almost angiomatous appearance.

The number of red cells does not, as a rule, reach the very high count of the cases of polycythæmia with splenomegaly recorded, although several cases ascending to 9,000,000 are given by Vaquez and Quiserne,[2] and Bernstein[3] reports a case of congenital cyanosis coming on at the sixteenth month, with death at two and one-half years, in which the red blood cells numbered 10,000,000, the liver and spleen were enlarged, the tricuspid orifice absent, and the right heart aplasic, with defective interauricular and interventricular septa.

The increase of the red cells is generally thought to be of the nature of a compensatory process, and has been compared to the polycythæmia of high altitudes. Grawitz suggests that it is only relative and due to the diminution of the water in the blood, as in the moderate cyanosis of acquired valvular disease. His "inspissation theory" is not proved. An increase of the marrow of the long bones, pointing to an increased formation of red cells, has been noted.

Polycythæmia is not a constant feature in congenital cyanosis; it is characteristic rather of the later stages of the disease, and its appearance is said to be unfavorable to the prognosis. Vaquez and Quiserne state their belief that where the polycythæmia reaches 6,000,000 it seems to be fatally progressive, evidencing a more and more insufficient aëration, the prognosis becoming correspondingly graver; "in such subjects one must look for a sudden change for the worse, and for the advent of those serious phenomena that precede death."

Diagnosis.—The cyanosis of congenital cardiac disease must be differentiated from a number of other forms. Of first importance among these is the so-called enterogenous cyanosis[4] (first described by Stockvis and other Dutch observers), in which the dark color of the blood is due to a sulphhæmoglobinæmia or methæmoglobinæmia, produced, it is thought, by the action of hydrogen sulphide or other toxic agents upon the blood. Again, certain aniline poisons lead to a methæmoglobinæmia giving a dark discoloration to the skin, and polycythæmia with splenomegaly is sometimes, although not always, associated with cyanosis.

[1] *Comptes rendus de la Société de biol.*, July 16, 1904.
[2] *Ibid.*, 1902, p. 915.
[3] *New York Pathological Society Reports*, February, 1906.
[4] A very able digest of enterogenous cyanosis, with a tabulated statement of all the recorded cases and full bibliography, is given by West and Clarke (*Lancet*, February 2, 1907). Other important articles on the subject are by Hymans van der Bergh (*Deutsch. Archiv f. klin. Med.*, 1905), Oliver (*Lancet*, December 29, 1906), Gibson on "Microbic Cyanosis," *Lancet*, July 14, 1906, and Blackader, *New York Medical Journal*, March 16, 1907, lxxxv.

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These conditions differ from congenital cyanosis in the slightly different tinge of the skin, which in methæmoglobinæmia is of a grayish hue, in polycythæmia with splenomegaly of a more florid aspect, by the absence of cardiac signs, by the presence of intestinal symptoms, and by the history of a toxic factor or the presence of enlargement in spleen and liver. In methæmoglobinæmia the red cells are not increased in number. Other conditions leading to cyanosis with clubbing are pulmonary emphysema, bronchiectasis, and adherent pericardium.

CLASSIFICATION.

Many attempts have been made to reduce cardiac anomalies to a scientific classification, but none have been entirely successful. The most logical arrangement is undoubtedly one based upon the stage of development at which the defect has occurred, differentiating those cases due to arrest of growth from those originating at a later period of intra-uterine life and apparently caused by fœtal disease. Peacock divides the cases into (*a*) those occurring in very early embryonic life, before the development of the septa (cor biloculare, etc.); (*b*) those of a more advanced stage, when the septa are already partly developed (septal defects, transposition, etc.); and (*c*) those of a later period after the embryo is completely formed (fœtal disease). Vierordt, following Rokitansky in his work on septal defects, makes a classification based on developmental principles so far as these are known, and subdivides stenosis and atresias of the valvular orifices into inflammatory and developmental forms, placing non-inflammatory stenosis and atresia of the pulmonary and aortic orifices with deviations of the aortic septum.

Our knowledge of the development of the heart is still too limited to permit of a complete classification on this basis, and, on the other hand, the etiology of a given condition is often impossible to decide in the individual case. Moreover, a grouping based on development alone is sometimes unpractical, for widely different pathological results may ensue from arrest of different parts of the heart at about the same period of fœtal life. For these reasons no one classification will be found adequate in its practical application, and it would almost seem that a grouping "on mixed principles" is the only one under which all the cases can be satisfactorily placed.

The 412 cardiac defects here studied present, either as the primary lesion or as a complicating condition, illustrations of practically all the cardiac anomalies known. In the following tables[1] of relative frequency, age, sex, etc., an attempt has been made to arrange these cases in as logical an order as possible.

[1] The sex is not always mentioned in the records of cases. The numbers in these columns do not, therefore, always correspond to the totals in the chart. When only two cases are included in a group the ages are placed in the maximum and minimum columns. When there is only one case the age is placed in the mean column.

The following abbreviations are used: F. O. = Foramen Ovale. I. S. = Interventricular Septum. D. A. = Ductus Arteriosus. Sys. = Systolic. Dias. = Diastolic. Pres. = Presystolic. "Double" indicates the combination of a systolic with a diastolic murmur.

The data given as to age, sex, and physical signs refer to the cases in the first column in the chart. This column added to the second to last column gives the total relative frequency of each defect, whether classified as primary lesion or as complicating other defects.

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CHART SHOWING RELATIVE FREQUENCY, AGE, SEX, CYANOSIS, AND PHYSICAL SIGNS IN 412 CARDIAC DEFECTS.

SUBJECT.	CLASSIFIED AS PRIMARY LESION.																					CLASSIFIED WITH OTHER DEFECTS.	TOTAL INCIDENCE.
	TOTAL.	AGE.			SEX.		CYANOSIS.			DYSPNŒIC ATTACKS.	THRILL.	MURMUR.											
		MAX.	MIN.	MEAN.	MALE.	FEMALE.	MODERATE.	MARKED.	CLUBBING.			SYS.	DIAS.	PRESYS.	CONTINUOUS.	DOUBLE.							
I. Anomalies of pericardium:																							
1. Absence of pericardium.	3	33	28	31	3	...	...	...	...	...	...	...	...	...	...	...						...	3
2. Diverticulum.	1	..	...	47	...	1	...	...	...	...	...	...	...	...	...	...						...	1
3. Localized defects.	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...						...	
II. Displacements of heart:																							
1. Ectopia cordis.	5	3 mos.	newb'n	21½d's	3	2	...	...	...	...	...	...	...	...	...	...						1	6
2. Dextrocardia.	5	28	75 dy's	19.6	2	3	2	...	1	...	1	1	...	...	...	...						2	7
III. Anomalies of the heart as a whole:																							
1. Bifid apex.	3	40	8	24	...	2	...	...	...		...	1	...	...	...	...						5	8
2. Diverticulum.	2	8	2½ mo.	4.1	...	2	...	1	1	...	...	1	...	...	...	...						...	2
3. Primary congenital hypertrophy.	3	14 mos.	newb'n	6⅓ mos	1	2	...	...	...	...	...	1	...	...	...	...						...	3
IV. Anomalous septa:																							
1. In left auricle.	5	48	25	38.2	3	2	...	...	...	...	...	...	...	1	...	...						2	7
2. In right auricle.	2	33	16	24.5	1	1	...	...	...	...	...	...	...	...	...	...						4	6
3. In ventricles.	2	39	2½	...	...	2	...	2	2	1	1	...	...	1	...	...						3	5
V. Defects of interauricular septum:																							
1. Patent foramen ovale.	10	60	11 mos.	23.2	4	6	6	2	...	1	..	3	...	...	...	2						124	134
2. Defects in septum above.	5	52	6	27	2	2	...	...	...	...	...	2	...	...	...	...						2	7
3. Defects in septum below.	10	56	14 mos.	23.4	4	5	3	...	...	1	3	5	...	1	...	...						4	14
4. Multiple defects in septum.	3	48	16	37	2	1	..	...	...	...	...	1	...	...	...	...						15	18
5. Distention of fossa ovalis.	2	...	...	54	...	1	...	...	...	...	...	...	...	...	...	...						7	9
6. Premature closure of f. o.	2	21 hrs.	fœtus	...	...	...	...	...	...	...	...	...	...	...	...	...						...	2
VI. Defects of interventricular septum:																							
1. At base.	32	42	at birth	0.5	14	13	11	3	...	4	10	19	...	...	...	4						117	149
2. Elsewhere than at base or multiple.	3	25	4 mos.	11	...	2	1	...	...	1	...	1	...	...	...	...						9	12
3. Aneurisms of undefended space.	5	53	24	41.7	4	1	...	...	...	...	1	2	...	...	...	...						2	7
Appendix: perforation of septum, inflammatory (?)	4	40	6	24.7	3	1	2	...	...	...	1	2	...	...	2	...						...	4

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VII. Combined defects of complete absence of cardiac septa:																		
1. Cor biloculare.	3	10 dys	44 hrs	5 dys	1	...	...	3	...	1	...	...	...	...	...	...	..	3
2. Cor biatriatum triloculare.	4	23	10 wks	6.4	2	1	2	1	...	2	...	...	...	...	...	2	4	8
3. Cor biventriculare triloculare.	1	1 mo.	...	...	...	...	...	1	...	...	...	...	...	...	...	...	4	5
4. Incomplete double heart.	4	3½	2 mos	1.3	2	...	3	...	1	1	...	2	...	...	...	...	2	6
VIII. Defects of the aortic septum:																		
1. Persistent truncus arteriosus.	8	12	24 hrs	4.1	4	2	2	3	3	2	1	1	1	...	...	...	4	12
Appendix: Communication between aorta and pulmonary artery.	6	37	6 dys	15.4	4	2	2	2	...	...	2	2	...	...	1	1	...	6
IX. Deviation of the aortic septum:																		
1. Complete transposition.	27	11 yrs	8 dys	8	14	3	9	9	2	2	...	8	...	...	...	...	...	27
2. Partial transposition (both trunks in same cavity).	13	35	12 dys	6.8	7	3	4	3	1	1	...	1	...	1	1	1	2	15
3. Corrected transposition.	4	24	9 wks	11.4	3	1	...	...	...	...	1	1	...	...	...	1	...	4
4. Deviation to right of aorta (rechtslage).	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	71	71
X. Pulmonary stenosis:																		
1. With closed passages: (*a*) of orifice; (*b*) of conus.	7	45	13	23.2	4	3	3	...	...	...	3	5	...	...	...	2	...	7
2. With patent f. o. closed ventricular septum: (*a*) of orifice; (*b*) of conus.	9	23	4	14.2	3	6	6	1	3	1	3	6	...	...	...	1	1	10
3. With closed f. o., defect of ventricular septum: (*a*) of orifice: (*b*) of conus; (*c*) conus separate chamber.	37	28	11 dys	9.7	21	12	5	24	19	10	3	17	...	...	...	4	5	42
4. With patent f. o., defect of ventricular septum: (*a*) of orifice; (*b*) of conus; (*c*) conus separate chamber.	22	20	11 mos	8	12	9	6	13	6	9	7	12	...	...	1	...	9	31
XI. Pulmonary atresia:																		
1. With closed ventricular septum.	6	6 mos	6dys	3 mos	...	3	...	6	1	...	...	2	...	...	...	...	2	8
2. With defect of ventricular septum, closed f.o.: (*a*) of orifice or conus; (*b*) conus separate chamber.	7	13	10 wks	4.3	3	2	3	3	2	2	1	3	...	...	2	...	...	7

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CHART SHOWING RELATIVE FREQUENCY, AGE, SEX, CYANOSIS, AND PHYSICAL SIGNS IN 412 CARDIAC DEFECTS—(Continued).

SUBJECT.	CLASSIFIED AS PRIMARY LESION.																		
	Total.	Age.			Sex.		Cyanosis.		Clubbing.	Dyspnœic attacks.	Thrill.	Murmur.					Classified with other defects.	Total incidence.
		Max.	Min.	Mean.	Male.	Female.	Moderate.	Marked.				Sys.	Dias.	Presys.	Continuous.	Double		
XI. Pulmonary atresia (continued)																		
3. With defect of ventricular septum, patent f.o.: (*a*) of orifice or conus; (*b*) conus separate chamber.	10	6	13 dys	3.7	5	2	3	5	2	...	...	3	...	...	...	...	4	14
XII. Pulmonary dilatation.	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	68	68
XIII. Aortic stenosis and atresia:																		
1. Subaortic stenosis.	5	38	9	20.2	3	1	...	...	1	...	2	2	1	...	...	...	2	7
2. Stenosis of orifice.	5	13	14 dys	3.5	1	2	2	...	...	1	...	2	...	...	...	1	1	6
3. Atresia of orifice.	3	15 wks	2 dys	6.2 wks	1	1	...	2	...	...	...	1	...	...	...	...	...	3
XIV. Anomalies of semilunar cusps:																		
1. Supernumerary pulmonary cusps.	8	80	15 mos	35.2	6	1	...	...	...	...	...	...	...	...	...	...	2	10
2. Supernumerary aortic cusps (double row).	2	34	2	...	1	1	...	...	...	...	...	...	...	...	...	2	1	3
3. Bicuspid pulmonary cusps.	1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	26	27
4. Bicuspid aortic cusps.	11	68	6 wks	32.5	9	1	...	...	...	...	...	1	1	...	...	1	15	26
5. Defect of pulmonary cusps.	1	...	...	5 dys	...	1	...	...	...	...	...	...	1	...	...	...	2	3
6. Defect of aortic cusps.	1	...	...	64	...	1	...	...	...	...	...	...	1	...	...	...	2	3
XV. Stenosis and atresia of auriculo-ventricular valves:																		
1. Tricuspid stenosis.	2	28	7 mos	...	1	2	1	1	...	...	1	1	...	1	...	...	5	7
2. Tricuspid atresia.	7	2½	6 wks	7.7 mos	1	2	4	3	...	1	...	3	1	...	...	...	5	12
3. Mitral stenosis.	1	...	...	19 mos	...	1	1	...	...	...	1	...	...	1	...	...	6	7
4. Mitral atresia.	2	14 wks	2 dys	...	1	1	...	1	...	...	...	...	...	...	...	...	1	3
XVI. Anomalies of auriculo-ventricular cusps:																		
1. Double orifice.	4	71	7 wks	31.2	3	...	...	...	...	...	...	...	...	...	...	...	...	4
2. Displaced orifices.	2	21	7 wks	...	1	...	...	2	1	...	...	1	...	...	...	...	...	12
3. Miscellaneous anomalies	2	44	15	...	1	1	1	...	...	1	...	1	...	...	...	...	17	19

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XVII. Patency and anomalies of ductus arteriosus:																		
1. Patency.	19	53	6 wks	12.5	7	9	3	3	...	...	...	7	1	...	5	1	87	106
2. So-called aneurism.	4	40	10	10.1	2	2	1	...	...	...	1	1	...	...	...	...	...	4
3. Absence.	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	6	6
4. Multiple or anomalous origin.	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1	1
XVIII. Coaretation of aorta:																		
1. Infantile type.	5	5 mos	at birth	1.25 mo	...	2	1	2	...	...	...	1	...	...	...	...	25	30
2. Adult type.	28	64	2¾	36¼	17	8	4	...	...	3	...	8	...	...	...	2	9	37
Appendix: Absence of aorta below left subclavian. P. A. forms descending aorta.	3	10 mos	fœtus	3⅓ mos	1	1	1	1	...	...	...	...	...	...	...	...	...	3
XIX. Hypoplasia of the aorta.	2	21	17	...	2	...	2	...	..	1	...		...	...	...	...	20	22
XX. Anomalies of aortic arch and branches originating therefrom:																		
1. Double aortic arch.	2	87	45	38	...	2	...	...	...	...	...	...	...	...	...	...	...	2
2. Right aortic arch.	1	...	...	fœtus	...	...	...	...	...	...	...	...	...	...	...	...	1	2
3. Right subclavian from descending arch.	4	...	...	44	...	...	...	...	...	...	...	...	...	...	...	...	1	5
4. Left subclavian from ductus arteriosus.	1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1
5. Miscellaneous.	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	19	20
XXI. Anomalies of pulmonary artery.	1	...	...	10	1	...	...	...	...	...	...	1	...	...	...	...	...	1
XXII. Anomalies of coronary arteries:																		
1. Anomalous origin from pulmonary artery.	3	60	42	...	2	1	...	...	...	...	...	...	...	...	...	...	...	3
2. Miscellaneous.	1	42	...	...	...	...	...	...	...	...	...	...	...	...	...	..	5	6
XXIII. Anomalies of systemic veins entering heart:																		
1. Persistent left superior vena cava.	3	25	5 mos	12.6	2	...	...	...	...	...	...	...	...	...	...	...	10	13
2. Absence of superior vena cava.	3	39	37	...	2	...	...	...	...	...	...	...	...	...	...	...	...	1
3. Displacement of superior vena cava.	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	
XXIV. Anomalies of pulmonary veins:																		
1. P. veins enter auricle as common trunk.	...	...	...	...	...	...	...	...	...	..	...	...	...	...	...	...	7	7
2. P. veins enter systemic auricle.	1	...	...	5½ mos	...	1	1	...	1	1	...	1	...	...	...	...	6	7
3. P. veins enter persistent left superior cava.	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1	1

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It thus represents an attempt at a detailed classification based on strictly anatomical principles and on development so far as this is known, but without regard to the etiology, which is so often obscure. Thus the group of stenosis and atresias of valvular orifices is subdivided, not into inflammatory and developmental forms and their subdivisions, with or without transposition or *rechtslage*[1] (Rauchfuss, Vierordt), but on anatomical considerations only, with regard to the seat of the stenosis and the presence or absence of septal defects.

The majority of cardiac defects are complicated, and it is often difficult, sometimes impossible, to say which is the primary lesion; many of the cases present other anomalies of equal importance with those with which they are grouped. A cross-index has therefore been made in the two columns next to the end, and the total relative frequency is to be found in the last column of the chart.

SYNOPSIS OF CLASSIFICATION USED IN TABLES, PAGES 338–341.

I. Anomalies of pericardium.
II. Displacements of heart. (Includes ectopia cordis and dextrocardia.)
III. Anomalies of the heart as a whole. Bifid apex, diverticulum, primary congenital hypertrophy.
IV. Anomalous septa.
V. Defects of interauricular septum.
VI. Defects of interventricular septum.
VII. Combined defects or complete absence of cardiac septa. Cor biloculare, cor triloculare, incomplete double heart.
VIII. Defects of the aortic septum. Persistent truncus arteriosus. Communication between aorta and pulmonary artery.
IX. Deviation of the aortic septum. Transposition, *rechtslage*.
X. Pulmonary stenosis.
XI. Pulmonary atresia.
XII. Pulmonary dilatation.
XIII. Aortic stenosis and atresia.
XIV. Anomalies of semilunar cusps.
XV. Stenosis and atresia of the auriculo-ventricular valves.
XVI. Anomalies of auriculo-ventricular cusps. Double orifice.
XVII. Patency and anomalies of ductus arteriosus.
XVIII. Coarctation of the aorta. Pulmonary artery forms descending aorta.
XIX. Hypoplasia of the aorta.
XX. Anomalies of aortic arch and its branches.
XXI. Anomalies of coronary arteries.
XXII. Anomalies of systemic veins entering heart.
XXIII. Anomalies of pulmonary veins.

[1] The term *rechtslage* is used throughout to describe in brief a deviation of the aorta to the right, so that this vessel arises in whole or in part from the right ventricle. This German word is applied extensively in English in this connection.

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ANOMALIES OF THE PERICARDIUM.

These are rare and of little clinical importance. The pericardial sac may be *absent*, as in some forms of ectopia cordis, or *defective*. In 3 cases of so-called complete absence, recorded by Baly,[1] Bristowe,[2] and Hughes,[3] all in adults, the pericardium was represented by a rudimentary crescentic fold on the right side of the heart, and the cardiac fold of the left pleura was also wanting, the heart and lung lying in a common sac. In Bristowe's case the left lung was firmly adherent to the adjacent parietes of the heart, and the rudimentary fold formed a diverticulum, the cavity of which communicated freely with the common sac, which contained nearly a pint of clear serum.

Diverticulum of the pericardium is reported also by Bristowe[4] in a woman, aged forty-seven years. A small lobulated flaccid bag continuous with the parietal pericardium, and the size of a pigeon's egg, projected into the cellular tissue of the anterior mediastinum and communicated with the pericardial sac by an ovoid orifice one-third of an inch long. Interiorly it was imperfectly divided by crescentic folds.

Localized defects of the pericardium occasionally occur.

DISPLACEMENTS OF THE HEART.

The heart may be displaced in various ways as a result either of acquired disease or of a congenital lesion. Such displacement may consist of a simple twisting of the organ on its axis, so that the lateral surface comes to lie more anteriorly, or it may assume a transverse or directly vertical instead of the normal oblique position. It may be so dislocated that it occupies quite a different position in the thorax, such as the median line or the right side of the chest (false dextrocardia), or even comes to lie outside of that cavity, being protruded from it through a defect in its wall (ectopia cordis). Finally, the organ itself may be not dislocated but transposed, its different cavities and vessels bearing a completely reversed relation to each other and to the body trunk (true dextrocardia).

Ectopia Cordis.—By this term is understood a displacement of the heart so that it passes out of the thorax and comes to lie either upon the outer surface of the body or in the abdominal cavity. Full bibliographical studies, with reports of cases, are given by Jones,[5] and recently by Ellis.[6] The latter, following Rauchfuss, divides the cases into (*a*) pectoral heart, with fissure of the sternum; (*b*) abdominal heart, in which the organ protrudes into the abdomen through a defect in the diaphragm with or without external tumor; and (*c*) cervical heart.

Pectoral Heart.—Protrusion of the heart in the median line of the thorax is always accompanied by a defect in the sternum. This may be

[1] *Transactions Pathological Society*, London, 1852, vol. iii.
[2] *Ibid.*, 1855, vol. vi, p. 109.
[3] *Proceedings Pathological Society*, Philadelphia, 1883, xv.
[4] *Transactions Pathological Society*, London, 1869, vol. xx.
[5] *Ibid.*, London, 1855, vol. vi, p. 98.
[6] *Proceedings Pathological Society*, Philadelphia, 1906, p. 36.

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a fissure above or below, or a complete cleavage, or the bone may be absent altogether. Where the defect in the sternum is inferior the pericardium is always present. Cleavage of the entire sternum is usually accompanied by the protrusion of other viscera besides the heart, and to this condition the term "gastroschisis" better applies.

Abdominal Heart (ectopia interna), in which the heart is protruded into the abdomen through a hole in the diaphragm, is illustrated by Deschamps' case of a soldier, whose heart was found to be in the left lumbar region, occupying the position of the left kidney. Wilson tells of a well-developed child, aged seven days, in whom the heart lay in the epigastric region beside the liver.

Cervical Heart.—In cervical heart the organ lies high up in the neck. Among 5 cases cited by Jones is one quoted from Breschet, in which the apex of the heart was united to the tongue, and most of the abdominal viscera lay in the thoracic cavity, both sternum and diaphragm being cleft in the median line.

Ectopia cordis is a very rare condition. It may be recalled that in the early embryo the heart lies far forward toward its cephalic end, and that the thoracic wall is formed in two lateral halves, non-union of which may readily occur. The existence of cervical heart, of pectoral heart with fissure of the sternum and absence of pericardium, or of gastroschisis, is not compatible with life; in abdominal heart, on the other hand, life is not necessarily shortened (witness Deschamps' case), and in pectoral heart with inferior sternal fissure and pericardium present it might with due care be indefinitely prolonged (Ellis). In Goode's[1] patient, a female dying on the sixteenth day, with fissure of the sternum below the manubrium and visceral pericardium present, the heart was oiled every three hours and was kept covered by a cardboard box, and the child did very well for a time. Ellis quotes a case reported by Lannelongue, in which a thin membrane covering the heart sloughed on the fifteenth day, and the outer skin covering the organ was successfully united by sutures. He suggests that such operative interference might be tried in suitable cases where the visceral pericardium is present.

Dextrocardia.—This term is applied clinically to all cases in which the heart is found displaced to the right side of the thorax. Pathologically, two different conditions must be distinguished. In the one the heart is simply displaced to the right, sometimes as a congenital malposition, but usually as a result of acquired disease; in the other the organ is also transposed or reversed upon itself in the body, those parts usually lying on the left coming to lie on the right side, the relation of its different structures to each other remaining unchanged. This last condition, which is always congenital, may be called for convenience true dextrocardia.

True dextrocardia, or transposition of the heart, is not very uncommon in combination with transposition of the other viscera, but as an isolated condition it is exceedingly rare. Schrötter analyzed all the cases available to him in the literature, and did not find a single one confirmed by autopsy which was not combined with transposition of the other viscera, or with some distorting defect making the relations uncertain, or which did not prove to be a simple dislocation of the heart to the right. Kriezer[2] collected from the entire literature 14 instances of apparently true congenital dextro-

[1] *Virginia Medical Semi-monthly*, 1904, p. 555. [2] *Berlin Thesis*, 1880.

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cardia. Of these, 5 were without autopsy findings, and of the remainder, 3 only are clear cases.

In this series there are 7 cases (2 classed as a complicating condition), all apparently of congenital origin, in which the heart lay in the right side of the thorax. Of these 7, 4 are a simple displacement to the right, which was due in 2 instances to congenital cystic disease of the right lung, with compensatory emphysema of the left. A fifth is one in which transposition of the heart is combined with transposition of the other viscera. There remain 2 cases in which the heart lay on the right with transposed cavities and vessels, in one of which there is no transposition of the other viscera, while in the other the liver only is transposed.

Of interest in this connection are 2 cases, one reported by Hickman,[1] the other a specimen presented to the McGill Museum by J. McCrae, of transposition of the viscera with only partial transposition of the heart, which maintained its normal position, the apex pointing to the left, the ventricles with the auriculo-ventricular ostia remaining unchanged, but the auricles and the great arterial trunks transposed, the pulmonary artery atresic, the auricular septum defective, and the ductus arteriosus patent. In McCrae's case the septum between the ventricles was complete, in Hickman's it was defective. In a third case, one of stenosis of the aorta at the isthmus and multiple defects of the interventricular septum, there was transposition of the pancreas, spleen, stomach, and intestines, but not of the heart or liver.

The cause of true dextrocardia, as of transposition in general, is very obscure, but it is of great interest as being an illustration of one of those anomalous conditions which cannot be ascribed either to simple inflammatory action or to arrest of growth. It is probably to be explained by an altered relation of the embryo to the primitive chorion, so that its right instead of its left side is placed nearer to the blood supply, and thus the usual conditions of the circulation are changed.

Dextrocardia, as well as complete transposition, is in itself of no clinical significance, and may only be discovered accidentally by physical examination, which reveals the altered area of cardiac dulness occupying the same position on the right as it normally does on the left side.

ANOMALIES OF THE HEART AS A WHOLE.

Bifid Apex.—Bifid apex, in which the apices of both ventricles project below the interventricular groove, may occur in the normal heart without other anomaly or complicating grave defects, and is not very rare. It is explained by Shattuck[2] as a trace still persistent of the primitive bitubular heart of very early embryonic life, and he points out that it is the normal condition in some of the aquatic mammals. Gegenbauer, on the contrary, explains cleavage of the apex as a persistence of the groove which appears externally with the development of the interventricular septum, and which is evanescent in man, but is permanent in the dugong. Bifid apex occurs three times in Thérémin's 106 cases and eight times in this series.

Diverticulum of the Heart.—The heart may be prolonged into a hollow process. Arnold[3] reports a female child aged two and a half months,

[1] *Transactions Pathological Society*, London, 1869, vol. xx, p. 88.
[2] *Ibid.*, 1891, vol. xlii.
[3] *Virchow's Archiv*, 1894, cxxxvii, p. 318.

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a subject of congenital lues and dying of otitis media, in whom the apex of the left ventricle ran out into a hollow process which bent around like a hook, its blind end projecting upward and to the left. Bifid apex and diverticulum of the heart are not of any clinical significance.

Primary Congenital Hypertrophy.—An idiopathic hypertrophy of the heart occurs in children, as well as in adults, as a result of overstrain or of obscurer causes. Böllinger designates as such all those cases in which neither valvular lesions nor the recognized hindrances to the blood stream, such as arteriosclerosis, nephritis, or emphysema, are present as the cause of the hypertrophy.

Recently a number of observations have been published in which this hypertrophy existed at birth. In 1896, Virchow,[1] referring to a case reported by Hauser of a heart weighing 62 gms. in a child dying at eleven months after prolonged whooping-cough, stated that the hypertrophy might also be congenital, and that he had seen several cases which he thought were due either to a slight valvular lesion, which might have been overlooked, or to a diffuse myomatous infiltration of the heart wall. In 1898, Simmonds reported the first clear case of primary congenital hypertrophy. In a newly born child which died during a protracted labor all the organs including the kidney were normal, but the heart was greatly enlarged, especially in breadth. It weighed 44 gms. (normal weight 19 to 20 gm.); the right ventricle was ¾ to 1 cm., the left 1 to 1¼ cm. thick. The *papillary muscles took no part in the hypertrophy*, but were thin and small, thus indicating that it was not due to overwork. Simmonds suggests that the hypertrophy may have been due either to some cause in early embryonic life, which later passed away, or to Virchow's diffuse myomatous infiltration.

Among typical cases of congenital cardiac hypertrophy without valvular disease, nephritis, or apparent cause, are those reported by Effron,[2] Hedinger, and Kalb.[3] In the last named, an infant with rickets dying suddenly at six months, there was a much enlarged thymus. This is a not uncommon finding, and it has been suggested as a possible cause of the hypertrophy, either by producing an irregularity of the heart's action by pressure from above, or indirectly by raising the blood pressure.

ANOMALOUS SEPTA.

These may occur in both auricles and ventricles and lead to the formation of the so-called supernumerary cavities. In the auricles they are very rare; no instance is mentioned in Vierordt's statistical work, and Borst, in a study of an anomalous septum in the left auricle, published in 1905, finds no reference to the subject in the German literature, but only among recent English writers.

Anomalous Septa in the Left Auricle.—Only a few cases are on record. In four in the *Pathological Society Transactions* the appendix is described as entirely cut off from the sinus of the left auricle by an anomalous septum. Besides these, there are in the literature at least 6 fully reported cases in which, in an otherwise normal heart, a membranous septum

[1] *Berliner klin. Woch.*, 1896, p. 679.
[2] *Zürich Thesis*, 1903.
[3] *Munich Thésis*, 1906.

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stretched across the cavity of the left auricle, dividing it into a right posterosuperior chamber, which received the pulmonary veins and contained the interauricular septum, and a left antero-inferior chamber containing the auricular appendix and the mitral orifice. The two chambers communicated with each other by an opening of varying size. A groove externally marked the insertion of the septum in the wall of the auricle.

Andral (quoted by Church) mentions the occurrence of anomalous septa in the left auricle, but the first case reported appears to be that of Church.[1] J. K. Fowler,[2] Martin, Griffith,[3] Potter and Ransom[4] give studies of cases, and various theories are advanced by these authors as to the origin of the malposed septum. Martin suggested that it represented a persistence of the embryonic ridge between the sinus receiving the pulmonary veins and the left auricle, and Fowler thought it might be due to an overgrowth of the tissue forming the valvula foraminis ovalis. Potter and Ransom acknowledge that no satisfactory explanation has been advanced.

Finally, Borst[5] reported a case, the careful anatomical study of which, viewed in the light of recent embryological knowledge, seems to throw much light on the etiology of the condition. In a woman aged thirty-eight years, dying with failing compensation, the heart was of a quadrate shape, the right ventricle much hypertrophied and dilated, and the left auricle also greatly increased in size. The valve of Vieussens and the Eustachian valve were prominent on the side of the right auricle, but on the left the valvula foraminis ovalis was entirely absent. The left auricle was divided into a large upper cavity receiving one left and four right pulmonary veins, and a small lower cavity containing the appendix and the mitral orifice. The dividing diaphragm ran from above, anteriorly and externally, downward, inward, and backward. It was defective below at its insertion, 1.5 cm. above the base of the posterior mitral cusp, where a round hole, 1 cm. across, was the only communication between the cavities.

Borst believes that the primary anomaly here was a displacement of the pulmonary veins to the right, so that they entered the upper wall of the primitive auricle *between* the septum primum and the septum secundum. As the latter closed in, the whole volume of pulmonary blood passed into the left auricle, and the septum primum was carried round in the growth of the heart to the oblique position which the anomalous septum (the persistent septum primum) now holds. He regards the aperture between the upper and lower cavities as the persistent ostium primum.

Anomalous Septa in the Right Auricle.—No attempt has been made to explain these embryologically, but it is probable that some displacement similar to that suggested by Borst in the case of the left auricle, possibly a deviation of the septum secundum or an overgrowth of the valvula venosa dextra, may hold good. Two cases are reported by Moore,[6] in which a shelf-like projection, apparently an abnormal development of the Eustachian valve, stretched into the auricle.

Anomalous septa may occur in an otherwise perfectly normal heart, or

[1] *Transactions Pathological Society*, London, 1868, vol. xix, p. 188.
[2] *Ibid.*, 1881, xxxiii, p. 77.
[3] *Journal Anatomy and Physiology*, 1902-03, xxxvii, p. 255.
[4] *Ibid.*, 1904-05, xxxix.
[5] *Verhandl. d. Deutsch. Path. Gesell.*, September, 1905.
[6] *Transactions Pathological Society*, London, 1882, xxxiv, p. 31.

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complicating grave defects. When uncomplicated they may give no sign of their existence, and all the cases quoted above were in adults who had reached middle life. If the septum, however, is well developed, it must hamper the blood stream. Church's case and Borst's were both in women aged thirty-nine years, who finally died of failing compensation. Borst's patient suffered from earliest youth from dyspnœa; a presystolic murmur was heard at the heart's apex on the first examination, which had disappeared four days before death.

Anomalous Septa in the Ventricles.—These have an entirely different origin from those in the auricles. The commonest form is a septum shutting off the conus from the sinus of the right ventricle, which probably represents arrest at an early stage in the development of the heart, explained by Keith as a "persistence of the lower bulbar orifice." Such septa have usually undergone much fibrous thickening, and have been ascribed by many observers to inflammatory contraction, but in a case reported by Böhm[1] all evidence of inflammatory action was absent, and the conus was separated from the sinus by a simple muscular ridge. In a specimen in the museum at McGill University (Fig. 36) the interventricular septum was absent, the tricuspid and mitral orifices entered a common ventricle which gave off the aorta, while an anomalous septum, perforated by a diamond-shaped opening, cut off a small rudimentary chamber (apparently the conus arteriosus of the right ventricle) lying at the right upper angle of the common ventricle, and giving off the pulmonary artery. There are records in the literature of 5 similar cases of an anomalous septum in a common ventricle in all of which, however, there was also transposition of the arterial trunks.

Still more difficult to explain than the above are 2 cases reported by MacKenzie,[2] in patients aged two and a half years and thirty-nine years respectively. The hearts showed three ventricles separated by incomplete septa, the arterial trunks being given off from the right and middle ventricles, while the left received the mitral orifice. The marked resemblance to the three-ventricled heart of the turtle suggests some early arrest of growth.

DEFECTS OF THE INTERAURICULAR SEPTUM.

Rokitansky classifies these defects into those occurring in the primary and those in the secondary interauricular septum. It is not always possible to distinguish in a given specimen which of these two the defect involves, but in a general way it may be said that in those rare cases in which it lies in the upper part of the septum it is usually in the septum secundum, while in those in which the septum is wanting in its lower part a defect of the septum primum exists (persistent ostium primum).

In this series of 412 cases the foramen was patent 134 times, and there were 39 true defects of the interauricular septum, of which 7 were in its upper and 14 in its lower part, and 18 were multiple. In 13 cases the septum was rudimentary and in 5 absent (cor biventriculare triloculare).

Patent Foramen Ovale.—The commonest form of defect of the interauricular septum is a permanent patency of the foramen ovale. This

[1] *Berliner klin. Woch.*, 1870.
[2] *Transactions Pathological Society*, London, 1880, vol. xxxi, p. 63.

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orifice, which in the fœtus is freely open, allowing the passage into the systemic circulation of the blood aërated in the placenta, usually closes soon after birth, but its persistence in adult life as a valvular slit is not at all uncommon, and can scarcely be considered abnormal. Among 711 adults Zahn found the foramen ovale open 139 times, and among 357 of these who were over forty years of age it was open 80 times. In Adami's records of 1374 autopsies at the Royal Victoria Hospital, the foramen was patent 199 times (14.5 per cent.).

A widely patent foramen ovale is, however, a true anomaly, allowing free communication between the auricles, and sometimes giving rise to serious disturbances in the circulation. It occurs sometimes alone, and frequently in combination with other defects. Of the 134 cases in this series in which the foramen ovale was said to be open, in 39 it was described as "small, slit-like, valvular," and in 23 it was designated simply "patent," leaving a total of 62 cases in which it was "widely patent," "admitting a shilling" (Peacock[1]), "admitting the index finger," "a goose-quill," etc., that is, in these it may be considered an anomaly. In 10 of these cases it was classed as the primary lesion; in the remaining 52 it complicated another defect, which in 26 instances was pulmonary stenosis or atresia.

Defects of the Interauricular Septum Above.—These are extremely rare and of obscure origin. Under the title "Vena Cava Superior Receiving two Pulmonary Veins and Opening into both Atria," Ingalls[2] has described a large defect, lying in the uppermost part of the interauricular septum, above and behind the (closed) foramen ovale, and just below the entrance of the superior vena cava, which vessel received two right pulmonary veins, and was so placed that it rode over the defect and looked through it into both auricles; the right cavities were dilated. Similar cases are reported by Wagstaffe[3] (2 cases), Chiari, and Hepburn. In Wagstaffe's second case, as in Chiari's, the foramen ovale was patent. In Chiari's case three right pulmonary veins entered the right auricle, and he considered their displacement to the right to be the primary anomaly, and the defect in the septum to be secondary, due to the increased amount of blood passing from the lungs into the right auricle. Ingalls suggested that the anomaly is due rather to a displacement to the right of the septum primum, which, growing upward directly opposite to the lumen of the superior vena cava, finds no auricular wall with which it may unite.

Defects in the Lower Part of the Interauricular Septum.—These, although also rare, are more frequent than are the last, and the error in development is better understood. The majority are explained as a persistence of the ostium primum, the septum primum having failed to descend and unite with the cushion between the auriculo-ventricular orifices. In this connection the work of Born on the development of the septum in two parallel planes growing downward from above should be recalled. Such a defect has a very characteristic appearance, which, once seen, can never be forgotten. It lies directly above the ventricles, may be of very large size, and is of a crescentic or semilunar shape, the thin lower border of the auricu-

[1] *Transactions Pathological Society*, London, 1860, xi, p. 68.
[2] *Johns Hopkins Hospital Bulletin*, 1907, xviii.
[3] *Transactions Pathological Society*, London, 1867, xix, p. 97.

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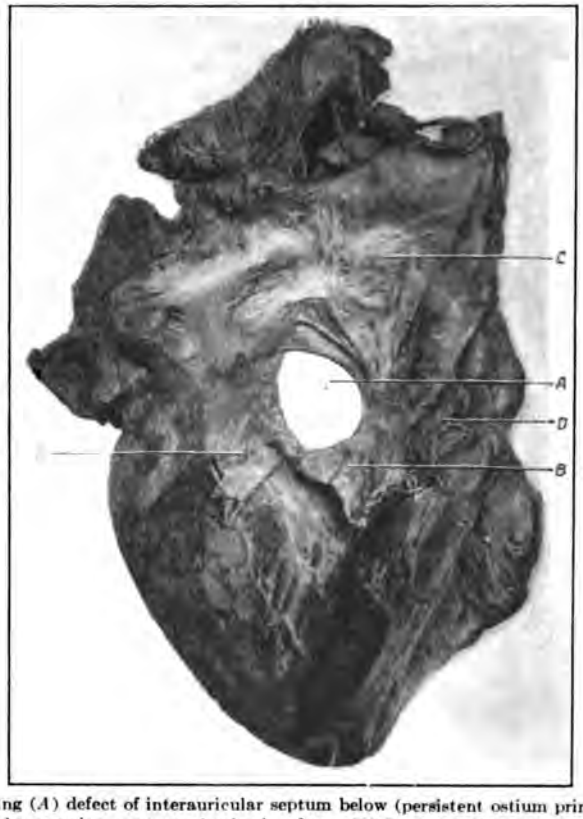
lar septum, which forms its upper boundary, arching across the venous ostia to join the lower margin formed by the bases of the mitral and tricuspid valves, which are commonly deformed.

A common and interesting associated anomaly is a division of the anterior segment of the mitral valve, which is cleft from its free border up to its insertion, the two parts converging here to an acute angle, being widely separated below. In 5 of the 7 cases of this defect reported by Rokitansky

FIG. 31



Heart showing (*A*) defect of interauricular septum below (persistent ostium primum), with (*B*) cleavage of right anterior segment of mitral valve. (*C*) Interauricular septum above showing closed foramen ovale. (*D*) Left posterior mitral segment. From a woman, aged thirty-two years, without cardiac symptoms, dying of perforative appendicitis. (From a specimen in the Pathological Museum, McGill University.)

this cleavage occurred. It is well seen in Fig. 31, from a specimen in the McGill Museum. Here the foramen ovale was closed, as in the cases reported by Griffith,[1] Söldner,[2] Moore,[3] Peacock, and Thomson.[4]

[1] *Manchester Medical Chronicle*, 1902, p. 383.
[2] *Munich Thesis*, 1904.
[3] *Transactions Pathological Society*, London, 1881, vol. xxxii, p. 39.
[4] *Proceedings of the Anatomical Society*, 1902–3, p. 36.

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In defects of the auricular septum below, and in widely patent foramen ovale, the pulmonary artery is often dilated, and there is sometimes a corresponding hypoplasia of the aorta. Atheroma of the dilated pulmonary and its branches also occurs. When the auricular septum is rudimentary, the defect is usually below, and a strand of tissue runs along the upper wall of the auricle, usually more to the left than to the right of the median line, indicating a division into a large right and a small left auricle. But sometimes the rudimentary septum lies below and the defect above, as in a case reported by Hebb,[1] in which it formed a crescentic ridge upon the floor of the common auricle, and one by Lucas of pulmonary atresia and anomalous septum in the right auricle, in which the auricular septum proper was "developed only below."

FIG. 32

Fenestrated membrane bulging into fossa ovalis. (From a specimen in the Pathological Museum, McGill University.)

Defects Elsewhere in the Interauricular Septum.—These may occur at any part. Rokitansky gives 6 cases in which the defect was below and behind, and the vena cava inferior looked through it into both auricles; and Peacock reports a large rounded aperture lying anteriorly, bounded by a thick band of muscle, behind which lay the closed foramen ovale. Ellis[2] mentions a similar one in a woman aged twenty-three years, dying of carcinoma of the uterus.

Multiple Defects.—The valvula foraminis ovalis is not infrequently perforated by numerous small openings, as in a specimen (Fig. 32) in the

[1] *Transactions Pathological Society*, London, 1890, xli, p. 56.
[2] *American Medicine*, 1906, p. 240.

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McGill Museum, and in several cases in this series. This recalls the fenestrated septum seen in birds, which is also present, according to Rokitansky, in the early human embryo, and suggests an arrest of development at this stage. In a case reported by Dublitzkaja[1] of combined defects of the auricular and ventricular septa, the auricular septum, defective below, "hung like a curtain over the common ventricle," there was a large patent foramen ovale, and also a large hole at the upper and posterior border of the valvula foraminis ovalis. Two specimens in the McGill Museum show combined defects above and below in the septum, and probably represent arrest at the stage of its development in which the ostia primum and secundum are present at the same time, and separated by a bridge of tissue.

FIG. 33

Bulging of fossa ovalis into left auricle. Valvular patent foramen ovale. (From a specimen in the McGill Pathological Museum.)

A curious aneurismal pouching of the fossa ovalis is sometimes seen (Figs. 32 and 33). It is described in nine cases in this series, in all of which the convexity of the pouch was toward the left auricle, indicating a rise of pressure in the right heart.

Symptoms.—A widely patent foramen ovale, or large defects in the auricular septum itself, may be present without giving any sign or symptom, and without interfering with the duration of life or the well-being of the individual. Tylecote[2] reports two cases of defects of the auricular septum

[1] *Zürich Thesis*, 1906, Case 2.

[2] *Lancet*, September 19, 1903.

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in mitral stenosis, in neither of which was there cyanosis or clubbing, nor were there any cardiac symptoms until failing compensation, with signs of the stenosis, became apparent a few months before death. In one, a woman, aged thirty-nine years, the auricular septum was entirely absent, excepting a small strand on the anterior wall of the auricle, and in the other there was a patent foramen ovale two inches wide; in both, physical signs and symptoms of the defect were entirely absent.

Such cases furnish an excellent illustration of the fact that venous and arterial currents can be mingled in the circulation without cyanosis as a necessary result. This is especially well seen in those defects of the uppermost part of the septum, in which the right pulmonary veins entered the superior vena cava or the right auricle. In none of these was there any symptom of disturbed circulation during life.

On the other hand, defects of the interauricular septum, even a patent foramen ovale, may give rise to serious symptoms of congenital cardiac disease, or may even in a few rare instances be the direct cause of death. Thus, in Simmons' case of a patent foramen ovale without other cardiac lesion, the child, aged eleven months, a Mongolian idiot, suffered always from paroxysms of dyspnœa, was cyanotic, and presented distinctive physical signs.

Not infrequently symptoms first develop after some event has embarrassed the pulmonary circulation. The picture is usually that of a relative mitral insufficiency in the stage of failing compensation. Marked cyanosis may supervene as a terminal event. Bard and Curtillet explain in this way a case in which cyanosis of an extreme degree developed during the course of a fatal bronchopneumonia; the foramen admitted a goose-quill. Hypoplasia of the aorta is not infrequent in defects of the interauricular septum. It is possible that it may, by itself leading to failing compensation, be the cause of the development of cardiac symptoms in some of the cases in which a patent foramen remains latent during earlier life. This was evidently so in Berthel's[1] case of a young man, aged twenty years, with a large patent foramen ovale and typical hypoplasia of the aorta, in whom the first cardiac symptoms developed after a long walking tour. In that of Ohm the caliber of the aorta is not stated, but the clinical picture was identical with that of uncomplicated hypoplasia of the aorta as described by many observers. It is readily understood that a patent foramen may exist without symptoms so long as pressure in the auricles is normal, but that the advent of regurgitation into the left auricle creates a vicious circle, the raised pulmonary pressure acting upon the right auricle and the increased volume of blood in its cavity upon the left.

Physical signs are frequently entirely absent, even in the large defects. A thrill, most intense over the middle of the cardia, is sometimes present, and was noted three times in this series. In large defects of the lower part of the septum the area of cardiac dulness is likely to be increased. Here also, especially when, as in persistent ostium primum, deformities of the tricuspid and mitral valves co-exist, the signs may be very complex. In a case reported by Moore a presystolic thrill was present, and loud systolic and presystolic murmurs were heard. In simple patency of the foramen a harsh systolic murmur localized over the left second and third, or third

[1] *Munich Thesis*, 1901.

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and fourth spaces, or diffuse over the whole heart, is most frequently described. The murmur may be double or presystolic in rhythm. *It is not transmitted along the pulmonary artery.* The murmurs may vary in intensity and character, and this is said to be a point of value in the diagnosis. In Ohm's[1] case the development of the double murmur of varying intensity was ascribed by him to a relative mitral insufficiency, the blood regurgitating into the right auricle from the left during systole, and impinging upon the sharp edge of the foramen.

When an organic mitral insufficiency exists with a patent foramen, the communication between the auricles may sometimes be diagnosed by the presence of a positive venous pulse in the neck, combined with the absence of the other signs of tricuspid regurgitation. This has been described as pathognomonic, but Ohm says this characteristic of the jugular pulse is not constant.

A serious clinical significance is given to patent foramen ovale by the fact that particles may be carried through the defect from the venous circulation to the arteries of the brain, or from the systemic arteries to the lung, leading to instant death. This possibility was first pointed out by Cohnheim in an observation of a woman dying of embolism of the middle cerebral artery. The foramen admitted three fingers, the arterial system was clear, while the primary thrombi lay in the veins of the lower extremities. Zahn first applied the term "paradoxical embolism" to this event in reporting a case which demonstrated Cohnheim's theory to be correct.

Ohm has collected 11 such cases from the literature in which an embolus from a thrombosed vessel or a metastasis from a new-growth has undoubtedly passed through the open foramen. He adds to an interesting study of the subject the report of a highly instructive case. Ballet[2] has collected 6 cases of death from cerebral abscess from infected emboli in which both cardiac and cerebral symptoms were present during life. In 3 of these there was a patent foramen, in 2 a defect of the interventricular septum.

Premature Closure of the Foramen Ovale.—In the first volume of the *Pathological Society Transactions* a condition is described by Smith, to which no other published reference is found; but a full account of an almost identical case occurs in Dr. Osler's handwriting in the autopsy reports of the Montreal General Hospital (P. M. No. 252, 1878). Smith's case was an infant, cyanotic from birth, dying at twenty-one hours. The foramen ovale was completely closed, and the much enlarged fossa ovalis pouched into the left auricle. The greatly dilated pulmonary artery carried the blood into the descending aorta through the distended ductus arteriosus. The right ventricle, mitral orifices, and valves were aplasic. Dr. Osler's case was a fœtus, stillborn about the eighth month. There was extreme anasarca of the whole body; the skin all along the groins and above the pubes had ruptured, and there were extravasations of blood forming great coagula in the cellular tissue of the neck. The foramen ovale was closed except for a small valvular slit at the side, which apparently did not permit the passage of blood, and the dilated pulmonary artery supplied the descending aorta through an enormously distended ductus arteriosus.

[1] *Zeit. f. klin. Med.*, 1907, lxi, p. 374.
[2] *Archiv. Gén. de Méd.*, 1880 (quoted by Ohm).

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DEFECTS OF THE INTERVENTRICULAR SEPTUM.

The interventricular septum may be completely absent (cor biatriatum triloculare), or it may be rudimentary, represented by a falciform process growing up from the lower and anterior wall of the ventricle, or localized defects may occur. These usually lie at its base, and are relatively common in association with other anomalies, but are not frequent alone. Defects elsewhere than at the base, whether alone or in combination, are among the rarest of cardiac anomalies.

Defects at the Base.—The cases of congenital cardiac disease here studied have been drawn only from reliable sources, and all have post-mortem reports attached, which should make them a fair index of relative frequency. It is therefore of interest to note that among them, while defects elsewhere in the septum are exceedingly rare, "pure" defects at the base are commoner than is usually supposed, and in combination with other defects they rank as the most frequent cardiac anomaly.

Among the 412 cases, a defect at the base occurred 149 times, elsewhere than at the base, 12 times, making 161 cases, or 39 per cent. Of the 149 defects at the base, 32 were classed as the primary defect and 117 complicated other conditions. Of the 32 "primary" defects at the base, 6 were combined with *rechtslage* of the aorta, and in 1 of these there was also hypoplasia of the pulmonary; in another there was pulmonary hypoplasia without *rechtslage;* in 1 there was a patent ductus arteriosus, leaving 24 "pure" defects at the base unassociated with *rechtslage* or other anomaly except (in 2 cases) bicuspid aortic valves.

Of the 117 defects at the base complicating other anomalies, 75 were in cases of pulmonary stenosis or atresia, in 53 of which there was also *rechtslage* of the aorta. Of the remainder, 20 were in transposition of the great trunks, 3 in other defects complicated by *rechtslage*, and 8 in persistent truncus arteriosus. That is to say, in 31 other cases the defect was associated with an irregularity of development of the great trunks. In the remaining 11 of these 117 cases, the septal defect was associated with tricuspid atresia in 6 cases, with mitral atresia in 2, with aortic stenosis or atresia in 2, and with partial defect of the aortic septum in 1.

Pathogenesis.—The combination of a defect of the interventricular septum with pulmonary stenosis and *rechtslage* of the aorta constitutes one of the commonest forms of congenital cardiac disease. So frequent is the combination that a causal connection between the three conditions has been sought, and rival theories as to which is the primary lesion have been suggested. One theory, first proposed by Meckel, was that the defect was primary, an arrest of development of the septum, and that the deflection of blood through it led to a secondary reduction in size of the pulmonary artery through disuse, and to a deviation of the interventricular septum to the left. Another theory, suggested by Hunter and Morgagni, was that the defect might be secondary, due to a rise of pressure in the right heart in a pulmonary stenosis of inflammatory origin, setting in before the septum had closed; and a third (Heine and Halbertsma), that the first anomaly was a deviation of the interventricular septum to the left, so that it failed to unite with the aortic septum.

No one of these theories satisfies all the facts. In opposition to the first,

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it may be recalled that a defect at the base is normally present at a certain stage of embryonic life, allowing of the free passage of blood through it, yet no alteration in the caliber of the pulmonary artery ensues. The second may hold in a limited number of cases where fœtal endocarditis, occurring before the end of the second month, has been the cause of the pulmonary stenosis.

Much light was thrown upon this whole subject by the work of Rokitansky, who concluded that non-inflammatory pulmonary stenosis, displacement to the right of the aorta, transposition of the great arterial trunks, and defects at the base of the interventricular septum were alike dependent upon a common cause, a deviation of the aortic, so that it failed to unite with the interventricular septum. He divided the latter into a part anterior, and one posterior to the undefended space, and classified defects at the base according as they lay in the anterior part of the anterior septum, in the posterior part of the same septum, or in the posterior septum. He pointed out that their usual situation was in the "posterior part of the anterior septum," that is, just anterior to the pars membranacea, in which case he believed they were practically invariably associated with a malposition of the arterial trunks. He maintained that this part of the septum was prolonged upward in the development of the heart to form the lowermost part of the right wall of the aorta, so that a failure of the aortic and interventricular septa to approximate with each other would lead naturally to a defect at this point.

Later observations by His and others have not confirmed Rokitansky's view of this extension upward of the interventricular septum to form the aortic wall, but show that the aortic septum is prolonged downward to assist in closing the interventricular septum at the undefended space. Moreover, independent defects of the interventricular septum, sometimes of large size, evidently not of inflammatory origin, and unassociated with any deviation to the right of the aorta, may and do occur. Such conditions cannot be explained on Rokitansky's theory as a deviation of the septa, but must be acknowledged to be a primary arrest of growth of unknown origin.

Pathology.—The commonest situation for the defect is directly beneath the aortic cusps and just anterior to the undefended space (Rokitansky's posterior part of the anterior septum) (Fig. 34). Here it lies with the fleshy muscular septum before it and the thin pars membranacea behind, and opens in the right heart beneath the septal and anterior cusps of the tricuspid, sometimes perforating them or bulging the (adherent) tricuspid leaflet before it, or opening into the right auricle directly above the base of the tricuspid, thus establishing a communication between this cavity and the two ventricles. More rarely the defect is placed farther forward in the septum in its anterior fleshy part just behind the front wall of the heart, and is separated behind from the undefended space by a muscular column, opening into the conus of the right ventricle just below the pulmonary valves (Rokitansky's anterior part of the anterior septum). Examples are given by Coupland[1] and Rolleston.[2]

Many writers state, probably on the authority of Rokitansky, that de-

[1] *Transactions Pathological Society*, London, 1879, vol. xxx, p. 226.
[2] *Ibid.*, 1891, vol. xlii, p. 65.

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fects of the undefended space itself are very rare, but a careful examination of recorded cases seems to show they are fairly common in this situation. The defect varies in form and size from a pinhead perforation with tendinous edges, a round or oval hole admitting a goose-quill, knitting-needle, index finger, etc., to a large triangular, semilunar, or crescentic space with thick walled lower muscular border, showing no sign of inflammatory action. In 2 cases only, 1 in the McGill Museum, the other reported by Tate,[1] a trumpet-shaped tube projected into the right ventricle behind the cusps of the tricuspid; it apparently began as a saccular pouching of the undefended space, which finally perforated at its apex into the right ventricle. In both cases there were marked physical signs.

Fig. 34

Defect of the interventricular septum at undefended space. Heart of infant. No other anomaly. (From a specimen in the McGill Pathological Museum.)

Owing to the greater force of the left ventricle, it is natural to suppose that the current of blood would be from left to right through the defect. That this is usually the case is shown by the oblique direction or funnel-shape it often assumes with its larger end toward the left ventricle, and by the not infrequent occurrence of fibrous patches on the opposite wall of the right ventricle. Hebb[2] reports a girl, aged eighteen years, dying of malignant endocarditis, with a heart showing a "pure" funnel-shaped defect at the base of the septum, admitting a goose-quill, and large vegetations on the aortic, mitral, and pulmonary valves, and *on the wall of the right ventricle opposite the defect.*

Septal defects may exist without producing any change in the heart chambers, but they lead, more frequently than do defects of the interauricular septum, to hypertrophy and dilatation of both ventricles, and especially of the right. Where the defect is combined with pulmonary stenosis and *rechtslage* of the aorta, marked hypertrophy of the right ventricle is a constant feature. The pulmonary artery may be dilated instead of stenosed, as in 9 cases of 32 "primary" defects at the base.

An anomalous muscle, said to have a direct etiological bearing upon defect of the base, is reported by Eppinger.[3] He calls it the musculus diaphragmaticus retromediastinalis, considers it a derivative of the diaphragm, and describes it as a unilateral striated muscle, varying in thickness from a pencil to a piece of twine, which lies within the left ligamentum pulmonis, arising from the diaphragm near the passage of the œsophagus, and inserted into the tissues of the posterior mediastinum at the level of

[1] *Transactions Pathological Society*, London, 1892, vol. xliii, p. 36.
[2] *Ibid.*, 1897, vol. xlviii, p. 41.
[3] LXVI *Versamm. Deutsch. Naturf.*, September, 1894.

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bifurcation of the trachea. It was present in 5 consecutive cases of primary defect at the base dissected for it; in these cases the heart was also slightly twisted from right to left, the right ventricle lying more anteriorly, the left more posteriorly; Eppinger suggests that the muscle, which runs over the left auricle to its insertion, hinders the normal turning of the heart, and that the twisting of the organ thus produced leads to a deviation of the septa, and so to the defect.

Aneurisms of the Undefended Space.—Aneurisms of the undefended space, sometimes of large size, bulging into the right ventricle, may occur, and are important in that they may give rise to marked physical signs. In a case reported by Hale White[1] an oval defect admitting a No. 10 catheter lay just below the right half of the anterior aortic cusp; its edges were thickened, but the septum around it for three-quarters of an inch was thin and translucent, and the sinus of Valsalva above it was expanded into an aneurismal pouch, which protruded and burst into the right ventricle. The author thought that the whole septum between the lower part of the aorta and the base of the ventricles was abnormally thin.

Defects in the Septum Elsewhere than at the Base.—These are usually multiple and irregular or slit-like in form (Rheiner, Preisz). They are of the greatest rarity. This is especially true of those low down in the septum.

Perforation of the Interventricular Septum.—Inflammatory.—In addition to congenital defects, acquired perforation of the septum, especially of the thin membranous undefended space, may occur after birth from extension of an endocarditic process. In a given defect it is often difficult or impossible to distinguish whether it be acquired or not, for endocarditis is very apt to attack the margins of a congenital lesion, leaving them fibrous, thickened, and distorted. A number of cases believed to be the result of a past inflammatory action are, however, recorded.

Symptoms and Physical Signs.—These may be entirely absent and the defect discovered only at autopsy. When cyanosis is present it may be slight or transient, appearing only on exertion, or terminal at the end of a long life, or, more rarely, and usually in those cases associated with *rechtslage* of the aorta, it may be well marked. Among the 32 "primary" defects at the base there was an entire absence of cyanosis in 16; it was slight in 8, moderate in 3, and marked in 3 cases.

Physical signs may also be absent, as in two otherwise normal hearts with defects admitting a goose-quill, in the McGill Museum; and Bennetz reports an infant, aged four months, with coarctation of the aorta, patent ductus, and large multiple defects of the septum, in whom the area of cardiac dulness was normal and the heart sounds were clear. On the other hand, physical signs atypical of acquired valvular disease are often present, even in the absence of symptoms, and are sometimes sufficiently characteristic to permit of a diagnosis being made. In pronounced cases there may be visible pulsation and precordial bulging, and a thrill, usually systolic in time and diffuse over the precordium, or most marked over the middle of the cardia, is fairly common. A thrill was present in no less than 10 of the 32 cases of primary defect, in 9 being systolic and in 1 a "continuous vibration." In 2 it was diffused over the whole cardia;

[1] *Transactions Pathological Society*, London, 1892, vol. xliii, p. 34.

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in 6 it was most marked over its upper half; in 2 others it was localized at the apex.

A harsh, systolic murmur localized in the third or fourth left space is the most frequent evidence of the defect. Sometimes a very small hole may be accompanied by a very loud murmur, as in Hillier's "tiny pinhead perforation." Roger described as characteristic a "single long, constant murmur beginning with systole and continuing through both heart sounds localized in the upper third of the precordial region." Reiss mentions as typical a loud systolic murmur in the middle of the precordium, localized over the inner part of the third left space and the fourth rib. Interesting cases of a "pure" defect with marked and characteristic physical signs having the above localization are reported by Thomson[1] and Carpenter.[2]

A murmur apparently due to the defect was present in 24 of the 32 cases. In those in which its character was specified it was loud in 16, rough in 3, whistling, grating, harsh, sawing, each in 1, rasping in 3; in 3 instances it was blowing. It was systolic in rhythm in all 24 cases, and in 3 of these a diastolic murmur was present as well. The point of maximum intensity was 11 times in the upper third of the precordium near the left sternal border; of these, in 4 it was stated to be at the third left space, in another also at the fourth left space, in 2 at the third costal cartilage (in one of which it was heard with equal intensity at the apex), in 2 at the pulmonary cartilage and second left space, and in one "over the middle of the sternum opposite the third left interspace." Besides these, in 3 other cases it was "along the left sternal border," "just to the left of the xiphoid cartilage," and "at the aortic cartilage;" in 2 (in one of which it was associated with *rechtslage*) it was "loudest at the apex," and in 4 it was diffuse over the precordium.

The murmur is usually transmitted downward along the left sternal border, and is frequently heard behind in the left infrascapular region. It may be diffused over the whole precordium, but is usually not heard in the axilla nor, according to Eisenmenger, below the clavicle. In 5 cases in this series it was so loud as to be heard over the whole chest, and in one case it could be traced into the vessels of the neck.

Eisenmenger claimed that the murmur produced by the defect is systolic, and that it may be transmitted along the aorta, and thus be heard in the vessels of the neck when hypoplasia of the pulmonary is also present, in which case the blood is diverted by the obstruction from its usual course into that vessel, and so passes from right to left into the aorta. He argued also that in ordinary cases without hypoplasia, in which the blood does enter the pulmonary through the defect, the murmur cannot be traced along its course because it lies too far beneath the surface, and so will not be heard above the base of the heart. In his own case, diagnosed by Schrötter before death, there was a defect admitting the thumb in the posterior part of the anterior septum, with *rechtslage* of the aorta and a dilated pulmonary artery. The patient, a man aged thirty-two years, had had cyanosis and dyspnœa from birth. There was visible precordial pulsation and bulging, and a systolic murmur over the middle of the heart transmitted everywhere over its surface, but chiefly to the right and inferiorly, not heard above its base along the course of the aorta nor in the pulmonary artery.

[1] *Edinburgh Hospital Reports*, ii, p. 293.
[2] *Reports for Study of Diseases of Children*, May 4, 1906.

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Aneurisms of the undefended space are frequently associated with marked physical signs, probably produced by the eddying of the blood. The localization of murmur or thrill is the same as in the defect itself.

COMPLETE ABSENCE OR RUDIMENTARY DEVELOPMENT OF THE CARDIAC SEPTA.

A rudimentary development of the cardiac septa leading to a diminution in the number of the heart's cavities should not be treated entirely apart from localized septal defects, being simply a more extreme degree of the same lesion. Yet the cases may be conveniently grouped together as indicating arrest at a very early stage of embryonic life, frequently associated with anomalies elsewhere, and forming an altogether different and more serious clinical picture.

Cor Biloculare.—When both the septa are absent, the result is a heart consisting of a single auricle and a single ventricle giving off a single arterial trunk. Cases of pure biloculate heart are extremely rare; two are recorded in the first volume of the *Pathological Society Transactions*, by Ramsbotham, in 1846, and Forster, in 1847. More commonly traces of one or both septa exist, indicating an attempted division into four cavities, the organ still remaining two-chambered in the exercise of its function. In the 2 instances given by Farre, and in 1 by Rosenthal, the ventricle and arterial trunk were single, but the auricles were incompletely divided by a rudimentary septum. In Wright and Drake's case[1] a slight muscular ridge on the anterior wall of the common ventricle represented a rudimentary ventricular septum, and a small band of tissue imperfectly cut off a small left from a large right auricle, while a tricuspid valve separated the auricle from the ventricle, from which arose a single arterial trunk. In a specimen recently presented to the McGill Museum (Fig. 35) by Dr. Andrewes, of St. Bartholomew's Hospital, the auricles are likewise imperfectly divided into a large right and a small left chamber looking like an appendage of the right, by a narrow septum having a large defect above, multiple fenestrations, and a deeply concave lower free border (persistent ostium primum). A thick muscular septum, one inch high, with rounded free border, projects upward from the lower wall of the ventricle, partly dividing it into a small, thick-walled right and a capacious left ventricle. A dilated aorta rides above this rudimentary septum, in front of which a narrow, thin-walled bicuspid pulmonary arises from a rudimentary conus. The small left opens into the large right auricle, and there is a common auriculo-ventricular orifice with five cusps, one of which is very strong and large, and seems to correspond, in part at least, to the anterior mitral segment, for its base coincides with the base of the left coronary aortic cusp. It arises from the opposing walls of either ventricle by heavy papillary muscles, and stretches across above the rudimentary septum in a remarkable way, shielding the common auriculo-ventricular from the two arterial ostia.

Another form of so-called biloculate heart may be illustrated by 2 cases reported by Crisp[2] and Turner.[3] In the latter there was dextrocardia, com-

[1] *Transactions Association American Physicians*, 1903.
[2] *Transactions Pathological Society*, London, i, p. 49.
[3] *Ibid.*, xxxiv, p. 32.

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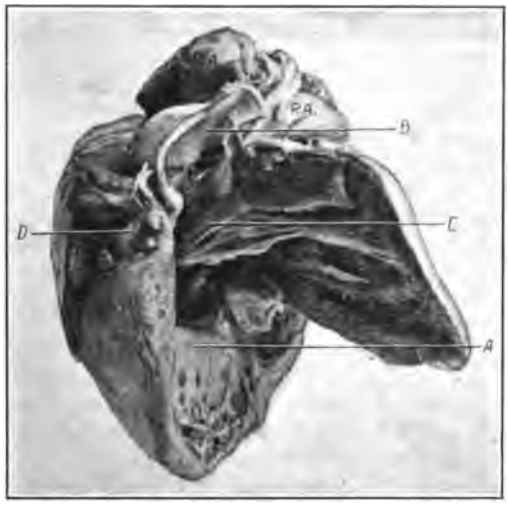
plete defect of the auricular septum, atresia of the pulmonary, which arose from the left side of the heart, and an aplasic left ventricle hidden among the muscular columns of the right or "single" ventricle. In Crisp's similar case there was no dextrocardia, but transposition of the atresic pulmonary and of the aorta.

Cor Biatriatum Triloculare.—Absence of the ventricular with presence of the auricular septum constitutes a three-chambered heart with two auricles and the tricuspid and mitral orifices opening into a common ventricle, from which (if the aortic septum develops), two arterial trunks arise. Arnold[1] reports a case of complete absence of the ventricular septum, with

FIG. 35



"Incomplete double heart," showing (*A*) the interventricular septum, defective in its upper half; *B*, a large, thick-walled aorta, arising from both ventricles above the defect; *C*, a single auriculo-ventricular cusp arising from both ventricles; *D*, stenosis of the conus of the pulmonary artery; *R.A.*, the enlarged right auricle. The right auricle and left ventricle are much hypertrophied and dilated; the left auricle and sinus of the right ventricle rudimentary. The interauricular septum is defective in its lower half. (From a specimen in the McGill Pathological Museum, presented by Dr. T. W. Andrewes.)

auricular septum defective below (persistent ostium primum), pulmonary atresia, dextrocardia, and absence of the spleen, and adds a study of 30 cases of cor biatriatum triloculare, the first of which was recorded by Chemineau, in 1669. In 6 of these the pulmonary artery was absent (persistent truncus arteriosus), in 11 it was narrowed, in 6 atresic, and in only 3 was it normal. The auricular septum was defective 18 times.

Holmes'[2] case (Fig. 36) and the 5 similar ones mentioned with it under Anomalous Septa are illustrations of a true cor biatriatum triloculare in which an anomalous septum cuts off the rudimentary cavity lying at the right upper angle of the common ventricle. This septum may be strong and muscular, and may either mark the persistence of the lower bulbar

[1] *Virch. Arch.*, xlii.
[2] *Transactions Edinburgh Medico-Chirurgical Society*, 1824.

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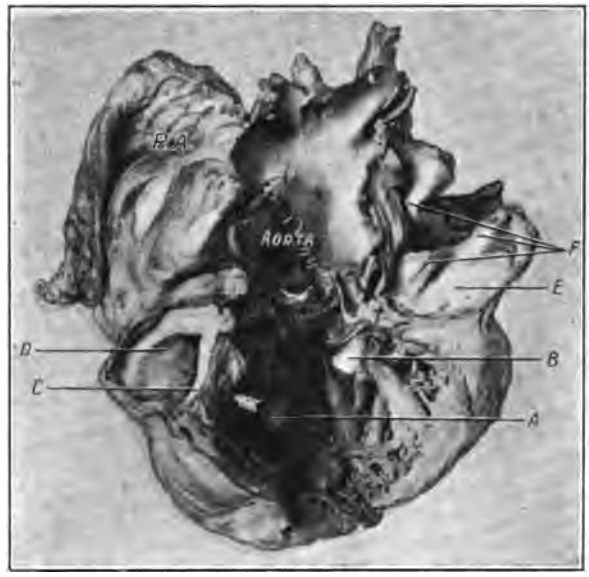
orifice, or, as seems more likely in the McGill specimen, it may be the defective interventricular septum itself carried round to the right in the growth of the heart (Fig. 36).

Cor Biventriculare Triloculare.—When the auricular septum is absent and the ventricular septum present, a heart with two ventricles and a single auricle results. Such a case is reported by Williams.[1] The pulmonary artery was atresic, and all the blood entered the common auricle through a single vein, the superior vena cava. When a rudiment is present,

FIG. 36



Cor biatriatum triloculare, showing (*A*) the tricuspid and (*B*) the mitral ostia entering, and the aorta arising from, the common ventricle. This is separated anteriorly by (*C*) a muscular septum from (*D*) a rudimentary cavity lying at its right upper angle, which gives off the dilated pulmonary artery. *E*, part of the rudimentary cavity (conus) which has been divided in laying open the heart, so lies to the left in the print; *F*, the pulmonary valve above it. The arrow passes through a diamond-shaped opening in the anomalous septum by which the blood enters the *R.A.* from the common ventricle. The right auricle is seen greatly dilated and hypertrophied. From a youth aged twenty-three years. (From a specimen in the Pathological Museum, McGill University, presented by Dr. Andrew Holmes, 1823.)

in those rare cases in which the strand of tissue lies *below*, as in Hebb's case, the effect of two ventricles and a single auricle is produced; when, as usually occurs, a strand of septal tissue lies along the upper wall of the auricle, the defect below is generally associated with defect of the upper part of the ventricular septum, so that the cases may be classed rather with imperfect biloculate heart.

Symptoms and Physical Signs.—Cyanosis is frequently present from birth, and may be very marked. Forster's,[2] Ramsbotham's,[3] and Crisp's

[1] *Journal of Anatomy and Physiology*, 1894.
[2] *Transactions Pathological Society*, 1846, vol. i, p. 21.
[3] *Ibid.*, p. 21.

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cases were all typical morbus cœruleus, dying, respectively, at seventy-eight hours, ten days, and ten weeks. On the other hand, symptoms may be very moderate, seeming scarcely proportionate to the pathological conditions that exist. In Turner's case, aged fifteen months, there was no cyanosis until just before death. Cases of cor biatriatum triloculare present perhaps the best illustration we have that the admixture of venous and arterial blood is compatible with long life and with only slight disturbance of the circulation. Young's patient, who died at thirty-nine years, cyanosis having developed only within the last three weeks of life, and Peacock's almost identical case, have already been noted. Holmes' specimen (Fig. 36) was from a young man, aged twenty-four years, in whom there was only moderate cyanosis and a tendency to suffocative attacks.

The same irregularity exists in the physical signs. In Wright and Drake's case there was cyanosis from birth, but no clubbing and no murmurs. In Dublizkaja's case, aged two and a half years, of "incomplete double heart," there was cyanosis and slight clubbing, but the heart sounds were declared "clear." On the other hand, Simmons describes a cor biatriatum trioculare in a child dying at two and one-quarter years, blue from birth, the apex displaced 1¼ inches outside the left nipple, and a loud, harsh, systolic murmur over the whole chest, most marked at the apex; no normal heart sounds were heard at any area.

DEFECTS OF THE AORTIC SEPTUM.

The primitive aorta becomes differentiated in very early embryonic life by the growth of a septum within its lumen into the two great vessels, one of which, the aorta, represents the fourth left embryonic arch, while the other becomes continuous with the sixth left arch as the pulmonary artery. When the aortic septum fails to develop, a single large thick-walled trunk (*persistent truncus arteriosus*) results, which arches upward in the course and gives off the branches of the normal aorta, the pulmonary artery being either absent or arising therefrom. This abnormality is very uncommon. Partial defect of the aortic septum is even less frequent than is its complete absence. It may result in a common trunk with early division into aorta and pulmonary artery and rudimentary septum within it, as in 2 cases by Rokitansky, or, when the defect is still smaller, in an abnormal communication between the aorta and the pulmonary artery or the conus of the right ventricle.

Persistent Truncus Arteriosus (Common Arterial Trunk, Complete Defect of the Aortic Septum).—This abnormality is very uncommon, but 18 cases have been available in the literature and from other sources of study. In persistent truncus the cardiac septa are frequently rudimentary or absent, a biloculate or triloculate heart existing. When, however, these are well developed and the heart is four-chambered and otherwise normal, a localized defect at the base of the interventricular septum always remains. The common trunk either rides above it, receiving the blood equally from both ventricles, or arises more or less entirely from the right ventricle, the blood entering it from the left through the defect. This recalls the early stage at which the arrest of growth has occurred,

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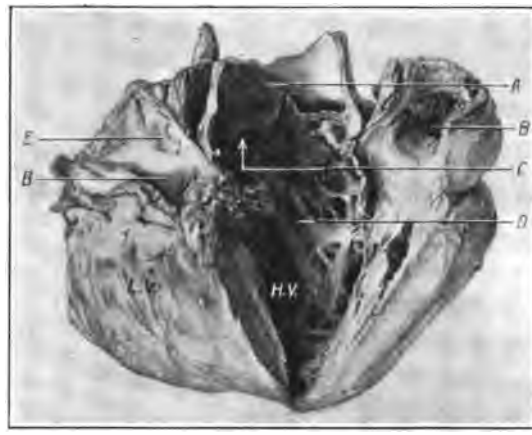
when the primitive aorta is given off entirely from the right side of the common ventricle (Fig. 27). A typical specimen of this kind is shown in Fig. 37 from a specimen in the McGill Museum. The large common arterial trunk springs entirely from the right ventricle, and has three strong semilunar cusps, behind two of which the coronaries arise. Below the anterior and right posterior cusps there lies a circular defect in the septum, admitting the little finger, with rounded edges, by which the left ventricle communicated with the right ventricle and with the aorta; a heavy muscular column runs from the anterior wall of the right ventricle to the lower border of this defect. The heart is wider than it is high (resembling very much in outer form that of a turtle); its right auricle and ventricle are very large and thick-walled, the latter forming the entire apex. The left chambers are perfectly formed, but smaller than the right,

FIG. 37



Persistent truncus arteriosus. Heart of a child, aged five years, in whom cyanosis developed at one and one-half years. *A*, common arterial trunk arising entirely from right ventricle, and communicating with the left ventricle through the right auricle; *B*, right auricle laid open; *C*, defect at base of interventricular septum; *D*, heavy muscular column from wall of right ventricle to base of defect; *E*, interauricular septum seen from right auricle showing multiple defects. Heart is wider than high. (From a specimen in the McGill Pathological Museum.)

and there are multiple small defects in the auricular septum. The aorta was cut off half an inch above its origin, and the blood supply to the lungs is unknown.

The pulmonary blood supply is of the greatest importance. Two large branches, one to either lung, may arise from the wall of the common trunk near its origin, as in 6 of the 18 cases, or as a single trunk from the same situation, or an artery may be given off at the site of the ductus, sending small branches to either lung; or the pulmonary artery may be rudimentary, as in Crisp's case, where several small branches descended to the heart and were lost upon its wall, or absent, as in Thérémin's second observation, where the small arteries arising at the site of origin of the bronchials were distributed one to either lung. The ductus arteriosus is absent in those cases in which the pulmonaries arise as branches of the aortic trunk.

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The common trunk is usually considered to be the analogue of the aorta, chiefly on account of the fact that the coronary arteries are given off from it behind the semilunar cusps. In one of Farre's cases, however, and in another almost identical by Forster[1] there were no vessels from the sinuses of Valsalva. The two large pulmonary branches arose from the back of the common trunk near its origin; a third branch gave off the great arteries of the neck, and a single coronary vessel descended from the concavity of the arch to the base of the heart, where it divided into the two coronary arteries. Vierordt thinks these are not cases of persistent truncus, but that the large vessel is the dilated pulmonary artery, and that the so-called single coronary that descends from the arch is the aorta atresic at its origin and connected with the pulmonary by a large patent ductus.

In Thérémin's second case the relative position of the semilunar cusps suggested that the common trunk represented the pulmonary rather than the aorta. Such resemblances are bound to occur, for it is to be remembered that the trunk includes in itself the origin of both vessels.

In a few instances in which the defect in the aortic septum appears to be only partial, the common trunk divides immediately after its origin from the heart, two-thirds of its lumen on the right forming the aorta, and one-third on the left forming the pulmonary artery, which takes its normal course.

This early division occurs in both of Rokitansky's cases, and in them the partial character of the defect is also proved by the presence of a delicate sickle-shaped septum within the undivided portion of the trunk, joining its wall between the left and posterior semilunar cusps behind, and left and right cusps in front. In Clarke's[2] case the trunk divided early, but there was no sign of a rudimentary septum within. Vierordt thinks that there is a radical difference between these cases of early division and those in which the branches to the lungs arise from the common trunk, in that here the sixth embryonic arch is persistent, whereas when the pulmonary is absent it must have undergone involution.

Symptoms and Physical Signs.—Much the same remarks apply to persistent truncus as to bilocular heart, for symptoms and signs are not always commensurate with the seriousness of the lesion. But here the condition is a still graver one and the average duration of life is much shorter. Crisp's case, a girl dumb from birth, with only slight cyanosis and clubbing, lived to twelve years, Forbes' to five years, Peacock's to thirteen months, and Buchanan's, a four-chambered heart with defect at the base of the septum, giving marked physical signs but no cyanosis, to six and a half months; all the others were marked cases of *morbus cæruleus* and died at birth or in early infancy. Vierordt quotes one dying at sixteen and another at nineteen years.

Communication between the Aorta and Pulmonary Artery.—(Partial Defect of the Aortic Septum).—A few rare cases have been described in which a circular or oval hole with perfectly smooth edges and evidently not of inflammatory origin lies in the anterior wall of the aorta a short distance above the semilunar cusps, and leads directly into the pulmonary artery shortly above its origin.

The first case reported was by Elliotson in 1830, and the second was by

[1] *Transactions Pathological Society*, London, 1846, vol. i, p. 48.
[2] *Ibid.*, 1885, xxxvi, p. 178.

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Wilks[1] in 1859. A fully reported case by Fraentzel[2] followed in 1868. Girard,[3] writing in 1895, was able to give only 3 cases (including Fraentzel's) from the literature in addition to his own, but Vierordt collects several others, among which are those of Baginsky,[4] Caesar,[5] and Rickards.[6] A recent valuable developmental study is that by Hektoen,[7] who gives a case of much interest and has collected 9 others from the literature.

The effect produced upon the circulation by the abnormal communication between the two great vessels is the same as in a patent ductus arteriosus, but the two conditions are quite distinct and have an entirely different etiology. This lesion is not a patent ductus abnormally shortened so that aorta and pulmonary artery have been approximated, with an apparent hole as a result. It is a true defect, as is proven both by its situation, which is much nearer to the origin of both arteries than is the ductus, and by the fact that in several of the cases reported the ductus has been present as well. Neither is the defect of an inflammatory nature, as is well seen in the smooth condition of its edges in the cases of Girard, Wilks, and Rickards, and from the character of the combined defects in the latter and in Fraentzel's case.

The abnormal opening is clearly a partial defect of the aortic septum, not at its junction with the interventricular septum, but higher up in its own substance. Two explanations have been offered, one that it is an exaggeration of the hollowing-out process that goes on normally in the wall of the aorta in the formation of the semilunar cusps, the septum becoming perforated thereby; the other, which seems to fit the facts better, that it is simply a failure of the aortic septum to unite with the wall of the common arterial trunk at a given point.

The first degree of partial defect of the aortic septum may be illustrated by a specimen in the McGill Museum of persistent ostium primum, double mitral orifice, and bifid apex (Fig. 42). The aorta and pulmonary artery have their normal external contour and lie in their normal relation, but are firmly united along their apposed surfaces and cannot be dissected apart, complete division by the septum having apparently not been effected within the trunks.

In all the recorded cases but one the hole lay in the aortic wall a short distance above the semilunar cusps. In that of Rickards the aortic segments were congenitally fused and the valve bicuspid with a circular funnel-shaped opening having smooth edges, admitting the little finger. This opening led into the pulmonary artery and lay behind the larger (fused) cusps. A triangular defect in the interventricular septum existed also.

Instead of opening into the pulmonary artery the hole may lead from the aorta into the conus of the right ventricle, as in the cases of Livingstone[8] and Cayla. In the second case of his article Hektoen adds a description of an anomalous opening from the aorta into the left ventricle through a defect at the base of one of the semilunar valves. This he ascribes also to a partial defect of the aortic septum.

[1] *Transactions Pathological Society*, London, 1860, xi, p. 57.
[2] *Virchow's Archiv*, 1868, xliii, p. 420.
[3] *Zürich Thesis*, 1895.
[4] *Berlin. klin. Woch.*, 1879, p. 439.
[5] *Lancet*, 1880, ii, p. 768.
[6] *British Medical Journal*, 1881, p. 71.
[7] *Transactions Chicago Pathological Society*, 1905.
[8] *New York Medical Record*, 1883, xxiv, p. 249.

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The pulmonary artery was larger than the aorta in Wilks' and Rickard's cases, a little smaller than in Fraentzel's and Girard's. Marked hypertrophy and dilatation of all the chambers of the heart, especially of the right ventricle, constantly results. In Girard's and Rickard's cases, in which there was no other cardiac lesion, the hearts weighed, respectively, 670 gms. and 23 oz. (651.8 gm.).

Symptoms and Physical Signs.—Cyanosis is not, as a rule, present, and there is no characteristic picture, excepting that an obstruction to the circulation is clearly manifest. All the cases recorded died before middle life with anasarca and other symptoms of chronic heart disease; those of Girard, Rickards, and Fraentzel reached thirty-seven, thirty, and twenty-five years respectively. Wilks' infant died at eight months, Hektoen's and Lebederber's at birth. Precordial discomfort, amounting often to actual distress, was present since childhood in Rickards' patient, as also in Fraentzel's and Girard's, and in the two latter there was dyspnœa on exertion and slight cyanosis. Physical signs may be absent or may be very marked, and they may vary, being sometimes quite atypical, or sometimes those usually associated with a patent ductus arteriosus. Owing to the great hypertrophy of the heart the cardiac dulness is usually much increased, especially to the right, and there is precordial bulging. Girard's case was characterized by a slight thrill and systolic murmur at the apex, which latter gave place later to reduplication of the first sound and distinct gallop rhythm.

A diastolic murmur is common. In Rickards' case the cardiac dulness was enormously increased, and there was an intense purring double thrill over the cardia, and murmurs, systolic and diastolic, running into each other as one continuous sound, were heard over the whole front and back of the chest, so loud as to be audible even through the bed-clothes; the pulse tracing was that of aortic regurgitation. In Fraentzel's patient, in whom there was a gaping opening 12 mm. across between the two vessels, and the right pulmonary artery arose from the ascending aorta, the heart was found to be greatly enlarged; both sounds were heard at all the ostia, and a systolic murmur was heard at the apex; in the fourth left space near the sternal border was a loud systolic and a long diastolic murmur, the latter heard with equal intensity over the base of the xiphoid cartilage. Both sounds and a diastolic murmur were audible in both second spaces, the murmur being louder and rougher in the second right space than in the left. Both sounds as well as systolic and diastolic murmurs were audible in the carotids, and "a systolic tone in the femorals."

DEVIATION OF THE AORTIC SEPTUM.

According to the teaching of Rokitansky, transposition of the arterial trunks, "rechtslage" of the aorta, and some developmental forms of pulmonary and aortic stenosis or atresia are due to irregularities in the development of the septum within the aortic bulb, or in its union with the interventricular septum. As this theory has been practically universally accepted, or at least has not been replaced by any other, the cases embraced by it will be considered here.

Transposition of the Arterial Trunks.—This may be defined as an alteration in the relative position of the two great vessels to the ventricles

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of the heart or to each other at their origin. A simple twisting of the vessels upon their axes, and also the deviation to the right of the aorta, known as *rechtslage*, are included by Rokitansky and Vierordt among the lesser degrees of this condition.

Pathogenesis.—This anomaly was first reported by Matthew Baillie in 1797. Early cases occur in Farre's work in 1814, and in the *Transactions* by O. Ward in 1851, Peacock in 1854, and Buchanan in 1857. Peacock, Pye-Smith, and others ascribed it to an irregularity in the development of the aortic septum, but until Rokitansky's work appeared in 1875, it remained a little understood phenomenon.

In some minor particulars the observations of Rokitansky upon development do not coincide with those of later observers; but it is in the elucidation of the complex and hitherto obscure subject of transposition of the arterial trunks that the epoch-making value of his great achievement may be said chiefly to lie. Rokitansky's explanation of transposition is one of those revelations in science astonishing one by its simplicity, and, as Vierordt remarks, he had the singular triumph of having supplied a working hypothesis that has not only explained the facts of his own experience, but has outlined and foreseen other pathological possibilities which have since been realized. He described and figured sixteen different forms of transposition, due, he believed, to different degrees and combinations of deviation or mal-union of the aortic and interventricular septa, some of which he had himself observed, others have since been recorded by later workers. Even if the advance of comparative embryology should unfold some other explanation of this subject, the verification of Rokitansky's brilliant hypothesis by the different forms of transposition seems to indicate that, so far as it goes, his theory is true, and that the growing knowledge of later times will amplify rather that supersede his solution of this difficult problem.

An entirely new theory has recently been suggested by Keith, to the effect that the explanation of transposition is to be found in the atrophy of the bulbus cordis around the pulmonary artery, and in its great muscular development about the origin of the aorta, where it normally undergoes involution.

The following is a brief statement of Rokitansky's theory of transposition: If the endocardial ridges, from which the aortic septum originates, arise in an abnormal situation, or if the direction of the septum be altered, so that its concavity, which normally lies to the right and posteriorly, faces in a different direction, the relative position of the pulmonary artery and the aorta (which is always the vessel toward which the concavity lies, and which is continuous with the fourth left embryonic arch) will be reversed, and transposition will result. All degrees of such a deviation may occur, the aortic septum being comparable to a movable disk, which may assume any relation within the common arterial trunk. But if it rotate through a full 180 degrees, the aorta and pulmonary artery will occupy exactly reversed positions, and if the interventricular septum be not also deviated, but maintain the same relation to the posterior trunk as in the normal heart, they will be placed in the reversed ventricles, the aorta arising to the left and in front and the pulmonary to the right and behind.

Again, in the normal heart, in the union of the aortic and interventricular septa, the latter becomes continuous with the left wall of the aorta in front and with its right wall behind (through the pars membranacea), surrounding

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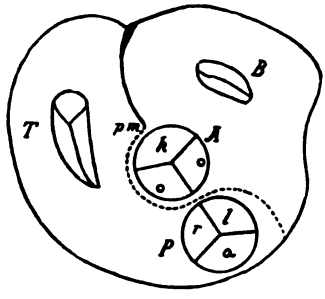
the vessel on its right side in such a way that the latter becomes placed in the left ventricle, while the pulmonary artery comes to lie in the right. Should this union take place at an abnormal angle, so that the interventricular septum surround the vessels rising posteriorly, on its left instead of its right wall, the trunks will be placed in the reversed cavities, and again, even though in this case the trunks may lie in a normal relation to each other, transposition will ensue.

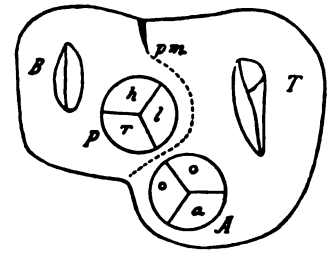
These two factors, a deviation of the septum within the aortic bulb and its faulty union with the interventricular septum, may occur in all degrees and combinations, giving rise to a corresponding number of different forms

FIG. 38



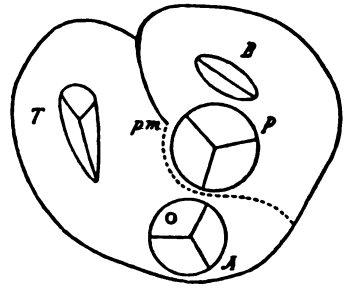
Normal relation.

FIG. 39



Corrected transposition.

FIG. 40



True transposition, vessels in reversed ventricles.

A, aorta; *P*, pulmonary artery; *T*, tricuspid valve; *B*, bicuspid valve; *pm*, pars membranacea; *p*, posterior cusp; *a*, anterior cusp; *lr*, left, right cusps (the small circles indicate the situation of the coronary article). (Republished from Vierordt, Nothnagel's System, 1898, xv, 1, 2.)

of displacement of the arterial trunks or of "*corrections*" of such displacements. Rokitansky distinguished two main classes (according as the transposition is "*corrected*" or otherwise by the interventricular septum), with eight subvarieties in each. Of the two main classes, his "Schema A" has as its type or starting point the normal relation, in which the concavity of the septum looks backward and to the right. The different subvarieties are constituted by the different degrees of deviation of the aortic septum rotating in an imaginary circle from right to left. The characteristic of the group as a whole is that the interventricular unites with the aortic septum

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in such a way that, although the trunks are altered in their relation to each other, they remain placed in their respective ventricles; that is to say, the transposition is "*corrected*" (Fig. 39).

In his second group, or "Schema B," on the other hand, the arteries arise throughout from the "reversed" ventricles; that is to say, the transposition is not "*corrected*" in the union of the interventricular septum. The type, or fundamental form from which the series starts, is the so-called *transpositio vera*, in which the septum has rotated through 180 degrees, so that its concavity looks downward and to the left, and the arteries lie in reversed cavities in the exact opposite of the normal position, the aorta to the left and anteriorly, the pulmonary to the right and posteriorly (Fig. 40).

Relative Frequency.—Transposition is said to be very infrequent, but it is probably commoner than is usually supposed, for, owing to the short duration of life in the complete form, the recorded cases are usually of infants, and in them the condition may often be overlooked. This is indicated by Thérémin's work. As a result of systematic observation of the autopsy material at the St. Petersburg Foundling Hospital, he describes, among 106 cardiac anomalies, 21 cases of transposition. In 1870 Kelley[1] found 40 cases recorded, and Vierordt, in 1898 (p. 47), mentions 76 among 383 cardiac anomalies analyzed by him. Since then cases have been reported by Ellis,[2] Rolly,[3] Ramm,[4] Thiele,[5] Emanuel,[6] Lochte,[7] and others, and there is a specimen in the McGill Museum. Among the cases tabulated in the chart there are 27 of complete, 13 of partial, and 4 of corrected transposition, making a total of 44 cases of transposition.

Pathology.—It is impossible to follow Rokitansky's minute classification in a statistical study of recorded cases, for the relation of the vessels to each other is often indefinitely stated. For practical purposes that into complete, corrected, and partial transposition, suggested by Vierordt (following Rokitansky), may be used.

(*a*) In *complete transposition* (Group B of Rokitansky) the vessels arise from reversed ventricles, the aorta from the right, the pulmonary from the left, as occurred in 27 of 44 cases. In 18 of these (15 from Thérémin, the rest from Kelley, Rolly, and Ramm) the aorta arose from the right ventricle to the right and anteriorly, the pulmonary from the left ventricle to the left and posteriorly. In one of Thérémin's observations the two great vessels arose side by side, but from reversed ventricles. The so-called *transpositio vera*, in which the vessels arise in exactly reversed positions from the reversed ventricles, the aorta from the right ventricle to the left and anteriorly, the pulmonary artery from the left ventricle to the right and posteriorly, is well illustrated by the cases of Pye-Smith[8] and Thiele. The pulmonary rode above a defect in the septum, and the aorta arose from the right ventricle in the normal position of the pulmonary artery in Thérémin's fortieth, forty-second, and forty-fifth cases, and in those of

[1] *Transactions Pathological Society*, London, 1871, vol. xxii, p. 92.
[2] *Proceedings Pathological Society*, Philadelphia, 1906.
[3] *Vierordt's Jahrb. f. Kinderheilkunde* (quoted by Ramm).
[4] *Kiel Thesis*, 1889.
[5] *Proceedings Anatomical Society*, 1902–03, p. 44.
[6] *Reports Society for the Study of Diseases of Children*, 1906, p. 241.
[7] *Ziegler's Beiträge*, Band xxiv.
[8] *Transactions Pathological Society*, London, 1873, vol. xxiii, p. 80.

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Lees and Rheiner. The aorta rose from both ventricles above the defect in the septum, the pulmonary from the left ventricle in that of Buchanan.[1]

(*b*) In *corrected transposition* (Group A of Rokitansky) the relation of the vessels to each other is more or less altered by a deviation of the aortic septum, but they are placed in their proper ventricles by the union of the interventricular septum. This is very rare; there are 6 almost identical cases described in which the aorta and pulmonary artery are completely reversed in their relation to each other, the aorta arising to the left and anteriorly from its own (the left) ventricle, the pulmonary to the right and posteriorly from its own (the right) ventricle (corresponding to Rokitansky's variation A 5). Two of these are reported by Rokitansky, one by Rauchfuss, one by Tönnies,[2] and two, not mentioned by Vierordt, are Thérémin's forty sixth and forty-seventh observations. In all 6 there is a defect of the interventricular septum at the base, and in all *the auriculo-ventricular orifices are also transposed*, the mitral lying in the right, the tricuspid in the left ventricle, and thus the "correction" of the transposition of the arteries by the septum as regards their relation to the auriculo-ventricular cusps is seemingly nullified; the aorta arises from a ventricle of venous form (in that it has a tricuspid valve), the pulmonary from an arterially constructed one. The frequency of this association of transposition of the venous ostia with "corrected" transposition of the trunks is commented upon by all the writers, but is not satisfactorily explained. Rokitansky suggests that "the ventricle in which the septum arises anteriorly forms as the arterial one." Fingerhuth[3] has described a case of corrected transposition with situs inversus of the viscera, and no transposition of the ventricles.

(*c*) *Partial transposition*, in which both vessels arise from the same ventricle or from a common ventricle in reversed relations, is relatively infrequent. *Both vessels may arise from the right ventricle*, as in Tooth's case,[4] in which a large thick-walled aorta arose from the usual origin of the pulmonary artery, which was itself small, thin walled, stenosed, bicuspid, and was given off from the right ventricle directly behind the aorta; the left ventricle was rudimentary and communicated with the right by multiple defects in the septum. A similar case is Thérémin's forty-first observation. *Both vessels may spring from the left ventricle.* Thus, Crocker[5] reports a girl aged thirteen years, with marked physical signs but with little cyanosis, in whom the pulmonary artery, small and constricted, arose from a small, thick-walled, left ventricle to the right and anteriorly, while the aorta arose from the same cavity posteriorly, and communicated with the hypertrophied and dilated right ventricle through a defect in the septum, which formed a canal ne inch long.

Both vessels may arise transposed from a common ventricle, as in Thérémin's forty-third observation, and in two examples of cor biatriatum triloculare with pulmonary atresia and transposition, reported by Turner and Crisp. Another example is in a bilocular heart in the Museum of the University of Toronto reported by Rudolf.[6] Here, in the heart of a subject aged about twelve years, a large, thick-walled aorta arises to the right and

[1] *Transactions Pathological Society*, London, 1857, vol. viii, p. 149.
[2] *Göttingen Thesis*, 1884. [3] *Zürich Thesis*, 1901.
[4] *Transactions Pathological Society*, London, 1883, xxvi, p. 127.
[5] *Ibid.*, London, 1879, xxxi, p. 92.
[6] *Proceedings Anatomical Society*, Great Britain and Ireland, February, 1900.

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anteriorly, projecting upward between the two auricular appendages, while directly behind and to its left lies a thin-walled pulmonary with a stenosed bicuspid orifice, the posterior lip of which is continuous with one of the cusps guarding the common auriculo-ventricular orifice, which lies directly below the pulmonary orifice, and enters the common ventricle entirely on the left side of the heart.

Finally, the transposed vessels may arise from a rudimentary cavity cut off by an anomalous septum from the common ventricle, as in the cases of Young, Peacock,[1] and Rokitansky (Cases 22, 23, and 24). In MacKenzie's case, with three ventricles, the vessels were transposed.

The semilunar cusps may be bicuspid, fused, or otherwise anomalous, but are usually normal in one, at least, of the transposed vessels. In 10 of Thérémin's cases of complete transposition they were placed as in the normal pulmonary and aorta, whereas in several other cases with identical relation of the great vessels, the aortic cusps were placed as in the normal pulmonary, the pulmonary as in the normal aorta. When the vessels lay side by side, as in his thirty-fifth observation, the cusps were lateral, two aortic lying on the left side and one on the right side, and *vice versa* in the pulmonary.

Slight degrees of deviation of the aorta may be recognized by a twisting of the cusps from their normal situation, so that their exact position should be carefully observed.

Of the first importance and interest are *the changes usually present in the relative size and thickness of the two great trunks*, for here is to be found, according to Rokitansky, another evidence of a deviation of the aortic septum. The pulmonary artery is frequently thin walled, small, bicuspid, and narrow, and the aorta dilated, but the reverse may be the case, and a large thick-walled pulmonary may be combined with a short and narrow aorta, as in Pye-Smith's case. Among Rokitansky's 24 cases of septal defect, in 18 there was transposition of the great arteries, and in 11 of these a stenosis or atresia of the pulmonary existed, in 3 a narrow aorta and a dilated pulmonary. Pulmonary atresia was present in the cases reported by Hickman, Turner, and Crisp.

In complete transposition the right ventricle, which gives off the aorta, is always hypertrophied and dilated, sometimes to an enormous extent, and both ventricles take part in the formation of the apex. The right auricle is usually hypertrophied and dilated also, and the left chambers may share in these changes, although to a less degree.

The Fœtal Passages.—In complete transposition the venous blood from the right heart will be distributed to the arterial system through the aorta, while the aërated blood entering the left auricle is returned again to the lungs by the pulmonary artery. The conditions of the circulation are thus of the poorest, and unless one or other of the fœtal passages remains open, life cannot be sustained. Usually a patent ductus, or a defect of the septum, combines with each other, or with a widely patent foramen ovale, to allow the passage into the aorta of the aërated blood. Very rarely do one of these conditions exist singly. Kelley, describing a case of complete transposition in a child aged three months, in whom the foramen ovale admitted a goose-quill but the ductus and interventricular septum were closed, says that this

[1] *Transactions Pathological Society*, London, 1854, vi, p. 117.

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state of the fœtal passages existed in only 4 of the 40 cases of transposition analyzed. In Kelley's case, and in 4 others of the 44 cases of this series, the foramen ovale formed the only communication between the right and left heart, namely, in Thérémin's twenty-seventh, thirty-fourth, and thirty-sixth observations, and in one by Emanuel. This last was remarkable in that the patient, who was the subject of cyanosis and clubbing, lived until his eleventh year. The interventricular septum was more or less defective in 23 of the 44 cases, that is, in 7 of the 27 of complete transposition. The defect was usually at the base, and was in all cases associated with a patent foramen and open ductus. In the remaining 21 cases of complete transposition the interventricular septum was closed. In 2 of these, that is, in Thérémin's thirty-seventh observation and in Ramm's case, the foramen was also closed, and a large patent ductus was the only communication between the right and left heart. In the latter the child was cyanotic from birth, and died on the fifty-sixth day. In 21 other instances the ductus was patent, and either the foramen ovale open or the septum defective. Coarctation of the aorta was present in 15 of Thérémin's 21 cases.

Symptoms and Physical Signs.—During the period of fœtal circulation transposition of the vessels is of little pathological significance, so that, unless associated anomalies be present, these subjects are born at full term, well developed, and apparently normal. Cyanosis may be apparent at birth, but is usually delayed, coming on after some days or weeks, developing possibly, as Thérémin suggests, as the ductus becomes obliterated. When pulmonary atresia is not present as well, the cyanosis is usually moderate in degree, becoming marked only on exertion or crying, and sometimes surprising one by its absence or by its very late appearance. In Thérémin's fortieth case, an infant aged twenty-six days, the entire absence of cyanosis was ascribed by him to the fact that the pulmonary artery arose transposed from the left ventricle, but received the blood from the right through a large defect in the septum. In Thiele's case, dying at three and a half years of bronchopneumonia, there was no cyanosis until the last illness, but defects of interauricular and interventricular septa combined to relieve the transposed vessels. Clubbing occurs, but is not a constant or prominent feature, for the cyanosis is usually of a moderate grade.

Physical signs are not characteristic, although in a few cases a successful diagnosis has been made. In Thérémin's thirtieth observation this was based upon "cyanosis increasing when the infant cried, hypertrophy of the heart both in vertical and transverse diameter, the heart sounds loud and accentuated but pure, the aortic and pulmonary sounds distinct." In Ramm's case, aged fifty-six days, a probable diagnosis was also made. Here also there was cyanosis from birth, becoming marked only on exertion, no murmur, no accentuation or reduplication of the heart sounds, but dulness extending beyond the right sternal border and upward to the second rib, of so marked a character that a mediastinal tumor was at first suspected. In Thérémin's thirtieth, thirty-first, thirty-eighth, and thirty-ninth observations the heart sounds were free from murmurs, although muffled, and cardiac dulness was increased to the right. On the other hand, a loud systolic murmur with maximum intensity at the apex was heard in Kelley's case, the same at the base and at the back in Pye-Smith's. In Lee's, aged seven months, a systolic at the left base developed at the fifth month, and in Buchanan's, dying at the fourth month, a loud, basic systolic murmur

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transmitted in all directions developed in the last year of life. In both the latter cases there was a defect of the septum.

A patent ductus or septal defect is usually present, and the physical signs produced by these conditions may obscure the *negative* character of the auscultatory phenomena, said to be characteristic of the clinical picture of an uncomplicated transposition.

Prognosis.—The duration of life varies in the three groups distinguished. In complete transposition it is usually very short; the age of eleven years was reached by Emanuel's patient, three and one-half by Thiele's, and four by Buchanan's. All the remaining twenty-four cases of complete transposition varied between seven months and a few days. In partial or corrected transposition, on the other hand, life may be much longer—Lochte's patient was seventeen, Tönnies' twenty-one, Young's thirty-six years. Vierordt gives the following analysis of the duration of life in 75 cases. To these are added the ages of 9 of the cases since recorded.

Age.	Vierordt.	New cases.	Total.
Born dead	3	0	3
1 to 24 hours	1	0	1
1 to 7 days	7	0	7
7 to 14 days	5	0	5
14 to 30 days	7	0	7
1 to 2 months	14	3	17
2 to 6 months	12	0	12
6 to 12 months	9	2	11
1 to 2 years	2	0	2
2 to 5 years	6	1	7
10 and 11 years	3	1	4
11 to 21 years	0	1	1
21 to 30 years	5	0	5
30 to 40 years	1	1	2

CONGENITAL STENOSIS AND ATRESIA OF THE PULMONARY TRACT.

Pulmonary stenosis is the form of cardiac defect most familiar to the practitioner. It is of much clinical importance on account of its comparative frequency, the relatively long duration of life, and the prominence of the cyanosis nearly always associated. To the student also it is a subject of the highest interest, for in its symptomatology and pathogenesis may be said to be focused the most difficult problems of congenital cardiac disease.

Owing to the wide variations in the conditions presented and the differing aspects from which the subject must be approached, a classification of the different forms is as difficult as it is necessary. Rauchfuss points out that the simple anatomical findings furnish the best guide to a useful grouping. Thus, the *degree of narrowing* is important, and a simple stenosis is to be distinguished from a complete atresia; from the standpoint of pathogenesis, the *seat and character of the stenosis* are criteria of much value; and thirdly, the *presence or absence of defects of the interventricular septum* provides a dividing line of the greatest importance. This last is the basis of Rauchfuss' classification, and is important etiologically as indicating the stage of embryonic or fœtal life at which the stenosis took place, and clinically in that the duration of life and symptomatology differ somewhat in the two groups. For these reasons the cases in the chart are subdivided along these lines.

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A division into inflammatory and developmental forms, while of the utmost theoretical importance, and a condition naturally to be aimed at in the study of the individual case, can only be attempted on the basis of these distinctions. The etiology remains in many instances at best a matter of conjecture.

Statistics.—Pulmonary stenosis is probably the commonest of all cardiac anomalies. The cases are scattered so freely through the literature that an exact statistical statement is impossible. Vierordt estimated at least 300 in 1898, and placed coarctation of the aorta next in frequency with 130 cases. Among 181 anomalies of the heart which he analyzed, Peacock found 119 of pulmonary defect. Keith examined 185 specimens of cardiac malformations in the different hospital museums of London, and found that in 135, or 70 per cent., there was an anomalous condition of the pulmonary tract, the deformity being in the conus of the right ventricle in 133 cases and in the pulmonary valve in 22. Among the cases of anomalies analyzed here, there are 119 of congenital pulmonary disease; of these, the disease was localized to the valve in 20 and was mentioned as involving the conus in 47. In the remainder the condition of the conus was not stated. The proportion of stenosis to atresia in recorded cases is stated as follows by different authors:

	Stenosis.	Atresia.	Number analyzed.
Kussmaul	64	26	90
Rauchfuss	81	33	114
Peacock	90	29	119
Vierordt	83	24	107
Thérémin	20	10	30
This series	90	29	119

The relatively high percentage of atresia in Thérémin's cases is explained by the fact that his material was entirely among infants, in whom the mortality from atresia is high.

The condition of the fœtal passages is made the subject of extensive statistical study by Meyer, Kussmaul, Taruffi, and other authors, of whose work a full review is given by Vierordt. A defect of the interventricular septum exists in the great majority. The number of cases with closed septum is relatively larger in atresia than in stenosis; thus Rauchfuss finds among 192 cases, 171 in which the interventricular septum is defective and 21 in which it is closed. Of these 21, 10 are cases of atresia and 11 of stenosis. Among Vierordt's 83 cases of stenosis are 71 with defective and 12 with closed interventricular septum; among his 24 of atresia, in 14 the septum was defective and in 10 it was closed. When the interventricular septum is entire, the foramen ovale is usually widely patent, but it also may in rare cases be closed.

Among the 90 cases of stenosis analyzed here the interventricular septum was defective in 73, and was entire in 17. In 10 of these 17 the foramen ovale was patent, but in 7 the auricular septum was also closed and no communication existed between the two sides of the heart.[1] Among the 29 cases of atresia the interventricular septum was defective in 21 and was entire in 8. Of these 8, in one the foramen ovale was also closed, but there was a large

[1] Cases reported by Reid, *Munich Thesis*, 1896, and from the *Transactions* by Ogle, vol. v, p. 19; Peacock, vol. x, p. 107, and xxx, p. 258; Hebb, vol. xli, p. 59; Ormerod, vol. xliv, p. 30.

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patent ductus. The ductus arteriosus is nearly always patent in atresia, but is usually closed in stenosis. Among the 75 cases of pulmonary stenosis classed as the primary lesion in the chart, the ductus was patent in only 7. Of the 23 cases of atresia, it was patent in 15. The condition of the cardiac septa in these cases with patent ductus was as follows:

	Stenosis.		Atresia.	
	Number analyzed.	Number with patent D. A.	Number analyzed.	Number with patent D. A.
F. O. and V. S. closed	7	0	1	1
F. O. patent, V. S. closed	9	1	5	4
F. O. closed, defect V. S.	37	2	7	3
F. O. patent, defect V. S.	22	4	10	7
Total	75	7	23	15

The abbreviations are as follows: F. O., Foramen Ovale. D. A., Ductus Arteriosus. V. S., Interventricular Septum.

Rechtslage of the aorta is present in the majority of cases with septal defect, and is especially frequent in atresia. Among the 59 cases of pulmonary stenosis with septal defect, classified in the chart as the primary lesion, it was present in 36 cases, in 25 of which the aorta arose from both ventricles above the defect, and in 11 chiefly or entirely from the right ventricle. Among the 17 cases of atresia with septal defect the aorta arose from both ventricles above the defect in 5, entirely from the right ventricle in 10.

Pathology.—Pulmonary Stenosis.—The narrowing may involve the whole pulmonary tract, or may be localized to the valve, artery, or conus. Two distinct types may be recognized:

1. In a few cases the stenosis is valvular in character and is produced by a thickening, shortening, or fusion of the pulmonary cusps. A thick diaphragm with three raphe of fusion on its arterial surface is usually formed, which protrudes into the pulmonary artery in a funnel-shaped way and is perforated by a circular or triangular opening of varying size. The pulmonary artery is frequently dilated above, may be normal, or somewhat thin-walled. The conus below the valve shares in the hypertrophy of the right ventricle, but is otherwise normal; the interventricular septum is usually closed. There is every evidence to show that the stenosis has originated in an inflammatory process in later fœtal life after the heart has been fully formed.

2. In the second and larger group of cases, the cusps may or may not be thickened or fused, but the stenosis is due to a rudimentary condition, hypoplasia, or deformity of some part of the pulmonary tract. In these cases a defect of the interventricular septum is usually associated and a deviation to the right of the aorta, so that this arises from both ventricles above the defect, or chiefly from the right ventricle, communicating with the left through the defect. Such forms, which seem to suggest a developmental origin, make up the great majority of cases of pulmonary stenosis, and the combination of these three conditions, pulmonary stenosis, defect of the septum at the base, and *rechtslage* of the aorta, is probably the commonest of all cardiac anomalies. Wm. Hunter published a case in 1783 and Farre commented on the frequency of the combination in 1814.

In the majority of cases—in Keith's estimate 90 per cent.—the conus of the right ventricle is involved in the deformity. Two distinct types of conus

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stenosis may be distinguished. The whole infundibulum may be more or less constricted, its musculature thickened, and the endocardium opaque. In a case of this kind, reported by Cautley,[1] the pulmonary cusps were delicate and healthy above the stenosis, but both they and the artery were very small. Usually the valves are thickened, fused, or rudimentary, and they are often bicuspid. Sometimes a thin diaphragm with delicate raphe showing no sign of inflammatory change, is stretched across the pulmonary orifice, suggesting an incomplete division of the endocardial cushions. In a case reported by Peacock[2] with small conus and thin-walled, short artery, the pulmonary cusps were absent, and an annular constriction, apparently muscular, reduced the orifice to the diameter of a crow-quill. In these cases a defect of the septum is almost invariably present.

A second group of conus deformities is that form in which a cavity, described by some of the older pathologists as a third ventricle, is cut off from the sinus of the right ventricle by a definite septum perforated by a small opening. Keith mentions some 50 such cases, 15 of which had come under his personal observation. There are 18 in this series, including one case of atresia. Keith describes and figures a remarkable illustration of this anomaly. The infundibulum is enormously dilated and communicates with the sinus by a small opening with thickened fibrous borders. The pulmonary cusps are large and competent, the artery dilated above, and there is a small defect of the interventricular septum. Another variation of this form of conus deformity is figured by Andrewes.[3] The conus is atrophied and is represented by a small cavity with thick muscular walls. It communicates with the sinus of the ventricle by an opening admitting a crow-quill one-quarter inch below the pulmonary cusps, which are small, bicuspid, and not thickened.

Hypertrophy and dilatation of the right ventricle and auricle are usually present in pulmonary stenosis, and are constant in the cases associated with defect of the septum at the base and *rechtslage* of the aorta. In these the hypertrophy is sometimes most marked in the wall of the sinus of the ventricle, indicating that it had been produced by the force needed to send the blood into the aorta through the defect, rather than by the obstruction in the pulmonary artery. The aorta is usually thick walled and of large caliber. In the developmental cases the pulmonary artery is usually narrow and thin-walled, resembling a vein in structure. When the stenosis is confined to the valve, the artery may be dilated.

Pulmonary Atresia.—All that has been said of the seat and character of the deformity in pulmonary stenosis applies equally to a complete atresia. In a small series of cases the point of obliteration is at the valve, the artery dilated above, the foramen ovale widely open, and the septum entire. In Weiss'[4] case the seat of atresia was in the conus, which admitted only a pinhead or a fine straw, and was lined by thickened endocardium; just above this were two fairly large pulmonary cusps, and the artery itself was comparatively large. There was a small patent foramen ovale, a large defect of the septum at the base, and a large thick-walled aorta arose from the

[1] *Edinburgh Medical Journal*, 1902, vol. xii, p. 257.
[2] *Transactions Pathological Society*, London, vol. xx, p. 87.
[3] *Ibid.*, 1865, vol. xvii, p. 45.
[4] *Archiv f. klin. Med.*, 1875, vol. xvi, p. 379.

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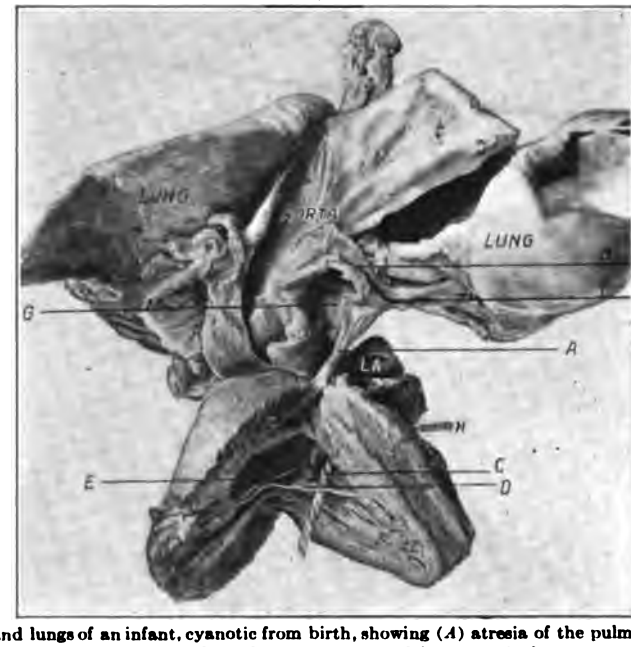
right ventricle above the defect. In a case reported by Saundby[1] the atresia seems to have been at the lower bulbar orifice.

The pulmonary artery may be obliterated for some distance above the valve, forming a fibrous cord, which may emerge suddenly from the fleshy outer wall of the ventricle and give no sign of its origin from within, or it may be patent throughout, diminishing toward the orifice in a funnel-shaped way. In such cases the cusps may be seen thickened and fused with each other at the bottom of the cul-de-sac formed by the artery, or they may form a triradiate elevation of three fleshy cushions; or no trace of them may remain. The aorta is usually very large, a true *truncus arteriosus*.

FIG. 41



Heart and lungs of an infant, cyanotic from birth, showing (*A*) atresia of the pulmonary artery; *B*, patent ductus arteriosus supplying lungs; *C*, defect of interventricular septum at pars membranacea, guarded by (*D*) an anomalous valve with false chordæ tendineæ; *E*, tricuspid orifice; *F*, left pulmonary artery; *G*, right pulmonary artery; *H*, cord passing through the septal defect; *LA*, left auricle. (From a specimen in the McGill Pathological Museum, presented by Dr. Osler.)

When a defect in the septum is present it rides over it, or in many cases arises entirely from the right ventricle.

The foramen ovale is frequently widely patent. It may be the only means of communication between the two sides of the heart, the interventricular septum remaining entire. Such cases are less frequent, and the condition is more serious to life than that associated with septal defect.

The alterations in the cavities of the heart vary with the condition of the interventricular septum. When this is entire the left ventricle is greatly

[1] *British Medical Journal*, 1877, vol. ii, p. 378.

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hypertrophied and dilated, and both auricles share in the enlargement, while the right ventricle undergoes a true concentric hypertrophy, its wall becoming greatly thickened and its cavity aplasic and lined with opaque thickened endocardium, or in some instances completely obliterated. When a defect of the septum exists, the right ventricle is greatly hypertrophied and is dilated as well, and the right auricle is correspondingly enlarged, the left chambers remaining relatively small. When the aorta rides over the defect in the septum, the left ventricle may share in the hypertrophy.

The Pulmonary Circulation.—When the pulmonary artery is obliterated the blood supply usually reaches the lungs through the widely patent ductus, but this is sometimes closed or absent. Meckel first suggested that in these cases the dilated bronchial arteries might perform this function, and this is usually the case. The lungs were supplied from the left subclavian in Chambers' case, from a dilated ductus arising from the left subclavian in Ramsbotham's. In a case reported by Voss two large bronchial arteries passed into each lung, and were accompanied by an anomalous branch from each coronary. Jacobson (1816) describes the bronchial arteries dilated, and a coronary artery dividing at the bifurcation of the trachea into two branches, one to each lung. Very interesting descriptions of the distribution of the new blood supply within the lungs are given by Weiss and Koller-Aeby. In the case reported by the latter the ductus was absent, and three large vessels, equalling the carotid in size, arose from the upper thoracic aorta at the site of origin of the bronchial arteries. The first turned to the right lung, following the bronchi; the others were given off as a common trunk, which divided into a larger branch going to the right and a smaller to the left lung.

Pathogenesis.—Two problems are presented. Is the stenosis of inflammatory or of developmental origin? What is the relation of the septal defect so often associated? In a consideration of the origin it must be recognized at the outset that a small group of cases occurs in which the stenosis is limited to the valves and no septal defect is associated; they present appearances identical with those produced by the chronic valvular disease of postnatal life. Such cases must be supposed to be the result of an endocarditis in later fœtal life.

In the large majority of cases a defect of the interventricular septum is associated, indicating that if the stenosis be due to an endocarditis, this must have occurred before the development of the heart was complete at the end of the second month of gestation. It is upon these cases that the discussion really turns. It is evident that if endocarditis can take place during the later stages of gestation, it may occur earlier as well. But, as Dr. Osler points out, it is not easy to imagine a fœtal endocarditis localized to so small an area as the pulmonary valves must be, before the eighth week of fœtal life. A further difficulty in proving the inflammatory theory lies in the fact that the presence of thickening and other changes in the valve does not exclude a developmental origin, for endocarditis is prone to occur at the seat of a cardiac defect. On the other hand, there are many cases in which the presence of associated defects and the absence of inflammatory action show positively that arrest of development has been the cause in these cases. Such considerations as these, and the increasing knowledge of embryology, have led gradually to the view, now held by most workers, that in the past far too great weight has been laid upon the part which inflammatory

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processes take in the etiology of the many forms of pulmonary stenosis which date back to early embryonic life, before the development of the heart was completed. The theory of fœtal endocarditis as a cause of congenital pulmonary stenosis, so warmly supported by Rokitansky in his earlier days, and so widely applied by Meyer and Kussmaul, must now be considered to be of but limited application. Among theories of the nature of the arrest of development must be mentioned that of Peacock. He noted a complete absence of the ductus in 2 cases, and collected some 12 others from the older literature. He suggested that the primary condition might be an atrophy of the fourth left branchial arch, and that the stenosis of the pulmonary might be secondary upon its disuse during the period of the fœtal circulation.

The frequent combination with defects of the septum and alterations in the relation of the two great trunks to each other led Rokitansky to ascribe the majority of cases, in which the pulmonary artery becomes of smaller caliber than the aorta, to a deviation of the aortic septum.

Reference has already been made to the entirely new and original theory recently communicated by Keith, who considers that in the majority of cases the stenosis is primary in the conus, and is the result of an arrest of development at a stage when there existed in the heart a fourth primitive chamber, the bulbus cordis. In accordance with the researches of Greil, he describes three changes as taking place in the evolution of the mammalian from the primitive heart of the fish and reptilia: (1) The division of the primitive auricle and ventricle; (2) the submerging of the sinus venosus in the musculature of the right auricle; and (3) the separation of the bulbus cordis from the left ventricle and aorta, and its complete incorporation in the right ventricle as the infundibulum of that chamber. This last change takes place by an upgrowth of the ventricular musculature around the cavity of the bulbus, the musculature of the latter being replaced by that of the ventricle, in the same way as the musculature of the auricle replaces a great part of that of the sinus venosus. The author considers that *"the submergence of the bulbus constitutes a critical phase in the developmental metamorphosis of the heart, and it is during this time that malformations are apt to occur."*

Four different types of conus stenosis are distinguished by him, of which the first is that well-differentiated form in which the conus forms a separate chamber, being separated from the sinus by a muscular partition. Peacock, in describing a similar case, compared it to the three-ventricled heart of the turtle, and considered that it represented an arrest of development. Keith explains the condition as being simply an arrest of development in which the infundibulum and body of the right ventricle have developed to a normal extent, while a constriction has remained between them, *representing the ventricular origin of the bulbus* or a persistence of the lower bulbar orifice.

The other forms of conus stenosis, in which there is a constriction more or less complete of the whole infundibulum, he explains as an arrest of development of the bulbus as a whole, its musculature failing to become submerged in that of the right ventricle proper.

The relation of the septal defect so often associated has been the subject of the liveliest discussion. The supporters of the theory of fœtal endocarditis have explained it as secondary to the stenosis, the rise of pressure in the right ventricle causing a current of blood to pass through the interventricular foramen, and so prevent its closure. Kussmaul, in a later development of this view, thought that the increased pressure in the right ventricle

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caused a deflection of the septum to the left, so that it failed to unite with the aortic septum. Meinertz, in reporting a case of defect in the middle of the interventricular septum and pulmonary stenosis, explains the latter as secondary, in the sense that it is due to a fœtal endocarditis induced by the presence of the defect.

On the developmental theory both stenosis and defect are concomitant effects dependent upon the same cause.

Associated Anomalies.—Grave cardiac defects are frequently associated, especially in pulmonary atresia, and constitute another argument in favor of a developmental origin. In Ettlinger's case there was a large defect in the interauricular septum above, with multiple defects of the interventricular septum, and the pulmonary veins opened into the right auricle. In Habershon's there was false dextrocardia, tricuspid stenosis, defect of the interventricular septum, and horseshoe kidney.

A fact of much importance is the presence of associated anomalies in cases of atresia with *closed* ventricular septum, which might reasonably be considered to be of inflammatory origin. It seems probable that the primary condition here was a narrowing of the conus or orifice in an arrest of development, and that the obliteration was produced by an endocarditis supervening in later fœtal life.

Symptoms.—The majority of cases of pulmonary stenosis and atresia present the classical picture of congenital cyanosis in all its details. So frequent is the association between the two conditions, that *morbus cæruleus* and pulmonary stenosis have been considered almost synonymous terms. The clinical aspects vary to a certain extent with the presence or absence of defects of the interventricular septum, and with the degree of deformity. In stenosis with closed septum cyanosis is usually slighter and of late incidence, and the duration of life much longer. The most typical instances of congenital cyanosis with bluish discoloration of the skin, becoming pronounced on exertion, clubbing of the fingers, dyspnœa, and cyanotic attacks are seen in the many cases in which pulmonary stenosis is combined with defect of the septum and *rechtslage* of the aorta. Pulmonary atresia differs from a simple stenosis in the more extreme degree of the cyanosis. These are the cases of true *morbus cæruleus*, in which a constant deep blue, or even purple, discoloration exists, increasing to black on violent exertion. Here the opposite condition in relation to septal defects is seen. When the septum is closed the cyanosis is more extreme and the duration of life correspondingly shorter. Pulmonary stenosis with defect of the septum in which no cyanosis is present is exceedingly rare, but a few cases are on record.

Physical Signs of Pulmonary Stenosis.—These are generally distinctive, but may be obscured by those of the septal defect so often associated. In typical cases, enlargement of cardiac dulness to the right and above, precordial bulging, epigastric and precordial pulsation indicate an enlargement of the right heart. Sometimes the cardiac impulse may be so violent that the head and neck share in the vibration of the chest. A thrill, localized to the second and third left spaces, or diffuse over the precordium, is fairly frequent. Its presence seems to depend somewhat upon the condition of the septa. Rolleston,[1] in reporting a case of stenosis with *rechtslage*, in which there was no precordial thrill, explains this by the

[1] *Transactions Pathological Society*, London, 1892, vol. xliii, p. 32.

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presence of a large defect of the septum, through which the blood current passed with ease into the aorta. He says that the evidence in recorded cases is contradictory upon this point, and suggests a statistical study of it. A thrill was present in 16 of the 75 "primary" cases analyzed. In these the condition of the fœtal passages was as follows:

PULMONARY STENOSIS.

Cardiac septa.	Number analyzed.	Number with thrill.
F. O. and V. S. closed	7	3
F. O. patent and V. S. closed	9	3
F. O. patent, defect V. S.	22	7
F. O. closed, defect V. S.	37	3

(F. O., Foramen Ovale. V. S., Interventricular Septum.)

That is to say, in a third of the cases with closed ventricular septum a thrill was present, as also in 7 of the 22 in which both foramen ovale and ventricular septum were open. But in the 37 cases with closed foramen ovale and with defect of the septum a thrill was absent in all but 3; in one of which there was a large patent duct, which was apparently the cause.

These figures are puzzling at first, but interesting on reflection, and are large enough to be of value as facts. The inference is, that a thrill is frequently present when the interventricular septum is entire, and also when a defect of that septum co-exists with a widely patent foramen ovale; when the interauricular septum is closed and the interventricular open a thrill is rare, and when it does occur may perhaps be ascribed to the associated septal defect. Further statistics are needed.

The pulmonary second sound is described as weak or absent in a certain proportion of cases. Much stress has been laid upon the absence of pulmonary accentuation as a diagnostic sign of pulmonary stenosis, but a number of cases occur, especially in the recent literature, in which the second sound has been distinctly louder than normal. In Cassel's[1] case the murmur was loudest at the apex, and the pulmonary second sound was marked. He remarks upon these points as indicating that a differential diagnosis between the different forms of congenital cardiac disease cannot be made.

A prolonged, harsh, rasping, or blowing systolic murmur heard over the whole cardia, but chiefly at the base, with its point of maximum intensity over the upper part of the sternum and the second left space, is present in the great majority of cases. It is transmitted upward toward the clavicle, along the course of the pulmonary artery, and over the sternum, but is faint or inaudible at the apex and to the right of the sternum. In a number of the cases analyzed it was heard also in the back in the left infrascapular region, but in all these a septal defect was associated, to which the transmitted murmur may have been due. It may be so loud as to be heard over the whole chest. From this type important variations occur. (1) The murmur may be heard over the whole cardia, but with maximum intensity at the apex, as in Cassel's case, a boy aged thirteen years, with pulmonary stenosis and a patent foramen ovale, but the ventricular septum entire. In a case of Peacock's there was a loud systolic murmur over the whole heart and along the sternum, the maximum intensity of which was at the inner

[1] *Berlin. klin. Woch.*, December 21, 1891.

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side of, and immediately above, the left nipple. In this instance a septal defect was associated. (2) In cases where the septal defect is present the murmur may be heard over the *aortic* area and *along the carotids*. Eisenmenger mentions this as a diagnostic point for the association of pulmonary stenosis with a septal defect. In Scheele's[1] case, a girl aged fifteen years, with marked cyanosis, the pulmonary orifice admitted a thin pencil, the valves were small and shrunken, the conus was reduced to the size of a pea, and the septum was defective at the base. Two pure tones were heard over the apex, and the second sound was accentuated at the aortic cartilage. There was a systolic murmur along the course of the pulmonary artery and at the left sternoclavicular articulation, which was transmitted far up the carotids and along both subclavians, and was most marked over the left carotid. It was heard also at the aortic cartilage. (3) The murmur may be heard in the back, in the left infrascapular region. This occurred in a number of the cases in this series, but in all a septal defect was associated, to which the transmitted murmur was probably due. (4) In a few cases physical signs are absent. Variot reports a child aged five years, with a large defect of the septum, and the pulmonary a small thin cord with rudimentary valves, who presented marked cyanosis with clubbing, but whose heart sounds were clear.

Diagnosis.—In the majority of cases the decided localization of murmur and thrill, the increased cardiac dulness to the right, the absence of pulmonary accentuation, and the presence of the distinctive symptoms of pronounced congenital cyanosis make a positive diagnosis possible. On the other hand, the variation in the character of the murmur and of the pulmonary second sound, and the occasional absence of cyanosis, render the diagnosis indefinite in a certain proportion of cases. That such atypical cases occur also makes it very difficult to exclude the possibility of pulmonary stenosis in the differential diagnosis of other cardiac defects. This is especially true of patency of the duct and of defects of the interventricular septum. The presence of constant and marked cyanosis, the less distinctive character of the murmur, and the fact that it is not usually heard in the back, are points in favor of stenosis. In patency of the duct, pulmonary accentuation is the rule, in pulmonary stenosis it is the exception.

Both the presence of the associated defect in the interventricular septum and the pulmonary stenosis have frequently been diagnosed. The presence of a thrill has been thought to speak rather for a closed septum, but this evidently does not apply when the foramen ovale also is patent. In a large number of cases the presence of the two distinctive murmurs can be easily traced, that due to the pulmonary obstruction heard best at the base and transmitted beneath the clavicle, that due to the defect localized at the fourth space, heard also in the back, both harsh, but of the two, the pulmonary usually of a more blowing character.

Course.—The duration of life in pulmonary stenosis with closed interventricular septum is relatively high. Peacock reports a patient dying at forty-five years, and the lowest age in this series was four years. The possibility exists in such cases that the stenosis has advanced, or even originated since birth. In stenosis with septal defect death occurs earlier, but adult life is also sometimes attained. The maximum age in this series

[1] *Deut. med. Woch.*, April 12, 1888.

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was twenty years. In pulmonary atresia life is very short. The patients with closed septum all die within the first few months. When a defect of the interventricular septum exists these subjects may live some years. The highest age recorded was thirteen years, in one of Peacock's cases.

The following table gives the duration of life in all the cases in the series in which this point is mentioned:

PULMONARY STENOSIS.

Age at death.	V. S. closed.	F. O. closed, defect V. S.	F. O. patent defect V. S.
Before 1 year	0	4	3
1 to 7 years	2	16	8
7 to 14 years	4	5	4
14 to 20 years	3	8	5
20 to 28 years	6	3	0
28 to 45 years	1	0	0
Number of cases analyzed	16	36	20

PULMONARY ATRESIA.

Age at death.	V. S. closed.	F. O. closed, defect V. S.	F. O. patent, defect V. S.
In first week	1	0	0
1 to 4 weeks	1	0	2
1 to 3 months	1	1	1
3 to 6 months	3	1	2
6 to 9 months	0	0	1
9 to 12 months	0	0	4
1 to 5 years	0	3	0
5 to 10 years	0	1	0
10 to 13 years	0	1	0
Number of cases analyzed	6	7	10

Many patients who survive until early adult life die, not of the lesion, but of pulmonary tuberculosis. The frequency of this disease in pulmonary stenosis and its grave prognosis can be no longer disputed. Much debate has taken place as to the cause of the predisposition which appears to exist. The most reasonable explanation seems to be: (1) The reduced blood supply to the lungs produces an anæmic condition there which favors infection; (2) the marked cyanosis usually present depresses the powers of resistance and tends to destructive tissue metabolism; (3) the subjects of pulmonary stenosis frequently live to an age when tuberculosis is likely to invade the organism when the nutrition is low.

This last point is illustrated in an interesting way in this series. Among the 16 patients with closed septum, in whom the duration of life was longer, pulmonary tuberculosis occurred 7 times. Among the remaining 59 patients with defect of the interventricular septum (in whom life was shorter) it occurred in only 8 cases, making an incidence of 15 cases in the 75.

Another not infrequent termination is by infection from an acute endocarditis developing at the seat of the defect. Robinson reports two instances in patients who both died at the age of twenty years, in both of whom the conus formed a separate chamber with narrow bulbar orifice. In the one case there were large vegetations on the conus wall, in the other these formed a fine fringe around its ventricular orifice, and coarse outgrowths about the associated defect in the interventricular septum. Acute endo-

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carditis appears to be especially common in this form of conus deformity, and among the 18 cases in which the conus formed a separate chamber, recent vegetations fringing the conus orifice, on the wall, or on the tricuspid valve were present in 6. These existed also in 8 others of the 92 cases of pulmonary stenosis. In Saundby's case there was a vegetative arteritis of the pulmonary artery, but none of the valves.

DILATATION OF THE PULMONARY ARTERY.

Dilatation of the pulmonary artery is very common in combination with cardiac anomalies, but is rare as an isolated condition. A few cases are recorded in which it appears to be primary and to originate in an irregular division of the common arterial trunk. The main vessel is diffusely enlarged and its branches are tortuous and dilated, but the heart and lungs are otherwise normal. The artery is usually dilated in defects of the lower part of the interauricular septum and in widely patent foramen ovale. In such cases hypoplasia of the aorta is frequently associated, and it is difficult to say which is the primary condition.

In defects of the interventricular septum at the base, the hypoplasia of the pulmonary artery so often present may give place to a marked dilatation. This was the case in 9 among the 32 primary defects of the septum in this series. Eisenmenger's case is an illustration in point. The pulmonary artery is also often dilated in transposition of the arterial trunks, patency of the ductus arteriosus, and in stenosis of the aorta at the valves or isthmus. The dilated artery may be atheromatous even in young subjects. When much enlargement exists, a thrill and murmur may be localized over its course, although the valves remain healthy and competent.

CONGENITAL AORTIC STENOSIS OR ATRESIA.

Subaortic Stenosis.—This term has been applied to a curious annular thickening of the endocardium of the left ventricle, a few millimeters below the aortic valves, which encircles the ventricular wall at this point and leads, in most of the cases, to a localized narrowing of the cavity. The cases recorded are not numerous, but the condition when present usually leads to serious clinical results, and it is therefore of importance. The thickened ring of tissue is often the seat of a chronic inflammatory process, probably of later incidence, so that it is difficult to distinguish its original character, but there can be little doubt that it is of congenital origin. Its peculiar localization and the fact that it always involves the base of the anterior mitral segment indicate this. The condition is usually considered to be analogous to the conus stenosis of the right ventricle. Keith explains it as an arrest of development, the bulbus failing to atrophy about the root of the aorta.

Endocarditis frequently develops both at the defect and at the aortic valves above it, and may thus lead to a further contraction at both points. Under the term "double aortic stenosis," Shennan[1] and Smart[2] report 2 such cases. In Shennan's patient there was a distinct calcareous ring 6 mm. in diameter,

[1] *Lancet*, January 7, 1905.

[2] *Ibid.*, November 19, 1904.

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which lay below the thickened and ulcerated aortic valves and extended across the anterior mitral segment. Most of the patients reach adult life. Slight symptoms may exist from childhood, or no sign of the presence of the defect may be given until an acute endocarditis develops or failing compensation sets in. The clinical significance of this condition lies in the frequent incidence of acute endocarditis. The picture is that of an acquired aortic stenosis.

Congenital Stenosis and Atresia of the Aortic Orifice.—These defects are so rare and the duration of life in them is so short that they are of little clinical interest. Moreover, their pathogenesis and pathology is so closely allied to that of pulmonary stenosis that they may be passed over very briefly. Two forms may be distinguished. Those apparently inflammatory, with valvular stenosis and ventricular septum entire, and those apparently due to an arrest in development. Unlike pulmonary stenosis, the inflammatory forms are here the commoner, fœtal endocarditis, although in itself rare in the left heart, usually involving the aortic orifice. Thérémin collected 17 cases, in only 2 of which was there a defect of the septum. Grave associated anomalies are especially common in these developmental forms of aortic stenosis.

In aortic atresia the left ventricle is very small and aplasic and, when a defect of the septum exists, may even be obliterated. The right ventricle is much hypertrophied and dilated, forming the whole apex. The foramen ovale and ductus are nearly always widely patent, the latter supplying the systemic circulation. In aortic stenosis, cyanosis is usually slight or absent. It is marked in atresia. Physical signs may be absent. A loud systolic murmur was heard in the 3 cases collected. In both of these conditions the duration of life is very short. In aortic atresia the highest age recorded is twenty-seven weeks (Vierordt). Simmons[1] describes an interesting case in an infant aged fifteen weeks, cyanotic from birth, with widely patent foramen ovale and ductus arteriosus, the left ventricle aplasic, the right ventricle greatly hypertrophied, and the aortic cusps fused to form a cone.

ANOMALIES OF THE SEMILUNAR CUSPS.

These cusps may be increased or diminished in number. They may be defective, fenestrated, or otherwise malformed. A row of supplementary cusps may exist, or they may be the seat of attachment of anomalous bands.

Increase in Number.—Supernumerary cusps sometimes occur in the pulmonary artery and, less frequently, in the aorta. A more or less perfectly formed fourth cusp of varying size, but frequently smaller than normal, may be inserted between two of the others. Or the usual number of segments may exist, and the sinus behind one of these be divided by a raphe which runs from the back of the cusp to the aorta, indicating fusion of the additional segment or imperfect division from its fellows. In rare instances five cusps occur. Peacock figures a case of five aortic cusps, two of which were fused with the others and the whole valve thickened. And Dilg[2]

[1] *Intercolonial Medical Journal of Australia*, February 20, 1906.
[2] *Virchow's Archiv*, 1883, xci, p. 193.

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enumerates from the literature 4 cases, in 2 of which the five cusps were in the aorta, and in 2 in the pulmonary artery.

The supernumerary cusps have sometimes been explained as an effort at repair of some inflammatory process of long standing, but when the fourth segment is perfectly formed, or the raphe indicating it shows no sign of thickening (as in a case in the McGill Museum), a true malformation must be concluded, which is usually explained as a formation by excess. Peacock suggested that it was due to an arrest of growth, a non-union of the two halves, from which he thought it possible the semilunar cusps might originate.

As this condition is of congenital origin, the cusps are generally so adapted to each other as to be competent to close the orifice, no insufficiency resulting; they occur usually in a heart free from other malformations, and are of very infrequent occurrence. Their clinical significance is thus slight, and lies chiefly in their tendency, like all valvular anomalies, to become the seat of a future endocarditis.

Diminution in Number.—A bicuspid semilunar valve at the pulmonary orifice is not uncommon in association with other cardiac anomalies, especially transposition and septal defects. A bicuspid aortic valve may complicate other defects, but usually occurs in an otherwise normal heart or associated with coarctation or hypoplasia of the aorta. In some instances both pulmonary and aortic valves may be bicuspid, as in Thérémin's one hundred and fifth observation.

The anomalous segments may be large, with smooth surfaces, showing no sign of further division, a true reduction in number existing; or one or both may present on the arterial aspect a ridge or raphe imperfectly dividing the sinus behind it into two parts, and indicating either a fusion of two formerly independent segments or a beginning separation of a single cusp into two elements; in other instances a single membranous ring or diaphragm may exist with two such raphes on its aortic surface, indicating the union with each other of all three cusps. Where such a raphe is absent, the condition is undoubtedly a true malformation, but where this exists, the origin of the bicuspid state of the valve admits of much discussion. Peacock[1] arrived at the conclusion that the majority of cases were congenital, due either to an original malformation or to fusion in a fœtal endocarditis. That such fusion may also occur later as a result of a postnatal endocarditis is admitted of course, but such recent cases are distinguished by the presence behind the fused cusps of a high raphe formed by their united adjacent portions, by the absence of compensatory changes in this and in the fused cusp, and by marked thickening, calcification, or other evidence of inflammatory action.

A series of cases illustrating the same line of thought was published by Osler.[2] As pointing to a fusion originating in fœtal life, he enumerates, (1) the presence of a low, sometimes half obliterated raphe, behind one of the cusps; (2) compensatory changes in the fused cusps, so that their free edge becomes equal to or even shorter than the single segment; and (3) the fusion of the coronary or right and left segments of the valve. That the

[1] *Transactions Pathological Society*, London, 1875, vol. xxvii, p. 59.
[2] *Montreal General Hospital Reports*, 1880.

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lateral (right and left) segments are the seat of congenital fusion, the posterior cusp remaining always single, is stated also by Birch-Hirschfeld.

When a thin, delicate raphe exists behind one of the segments of a bicuspid valve without any trace of thickening, Babes insists that it cannot be ascribed to a fusion in fœtal endocarditis, but must be regarded as a true malformation, probably an incomplete division of an originally single cusp. The development of the semilunar cusps is not yet clearly understood, but it is thought that they originate as two endocardial ridges, one on the right, the other on the left wall of the aorta, each of which is divided into two by the descent of the aortic septum, a third segment developing later in either artery. This theory would explain such cases as the above, and also the statement that so-called congenital fusion always involves the coronary or lateral cusps.[1]

Thickening of cusp and raphe does not prove fusion of inflammatory origin, for endocarditis is likely to supervene on any valvular anomaly. On the other hand, it has been pointed out to the writer by Dr. Adami that primary postnatal fusion may reasonably be deduced when (1) the two sections of the cusp are approximately equal; (2) when the raphe dividing them has its superior origin on a level with the superior origins of the unaffected cusp (instead of at the lower level, as referred to by Osler); and (3) when in addition the only thickening observable is in the angle between the fused cusps. It must be recognized that the free part of the cusps, being in constant motion, is but little liable to undergo inflammatory adhesion, and that this will be prone to occur at the point of their insertion into the aortic wall, which is the only portion of their edge that is fixed and relatively motionless. Therefore, inflammation originating at the angle of junction of contiguous cusps might lead to localized fibrinous and later to organized obliteration of the primary angle, or, in other words, to fusion of the cusps with a new immovable angle of junction further removed from the aortic wall, a progressive fusion occurring.

The results upon the heart and circulation of a reduction in the number of the aortic cusps may be summed up as follows:

1. The segments may approximate and be perfectly competent, no pathological effects ensuing. This is proven by the occasional finding of a bicuspid valve in healthy adults even of advanced age.

2. The gradual bulging of the cusps, their greater length, the free space that sometimes exists between them, perhaps a yielding of the aortic ring, lead frequently to a valvular insufficiency or to a narrowing of the orifice.

3. Endocarditis commonly supervenes, either as the acute, often malignant form, or as a chronic inflammatory process, leading to thickening and deformity of the cusps and to subsequent valvular disease.

4. Atheromatous changes at the base of the aorta have been frequently noted, and in 6 of the 11 cases described by Babes and Deteindre there was an aneurismal bulging of the right posterior wall of the aorta, which formed in 5 instances a definite aneurism, from the rupture of which, in 2 cases, death ensued.

This remarkable combination of an aneurism of the base of the aorta with a bicuspid valve is believed by Babes to be directly connected with

[1] Thérémin's ninety-sixth observation of a persistent truncus arteriosus containing four cusps, the two posterior of which each had two corpora Arantii, speaks against this theory of development.

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the bicuspid character of the aortic cusp below it, and is ascribed by him (*a*) to an extension of the same thinning or trophic process that led to the anomalous condition of the cusp, (*b*) to the lack of support given to the aorta at this its weakest point, and (*c*) to the frequent insufficiency of the cusps and the yielding of the aortic ring.

Miscellaneous Anomalies.—Dilg reports a remarkable case, in a child aged two years, of an endocardial fold divided roughly into two cusps with their convexity toward the ventricle, just below the base of a bicuspid aortic valve, both coronaries being behind one cusp. Banks[1] reports a woman, aged thirty-four years, dying suddenly, with physical signs of aortic insufficiency and a loud, musical murmur at the base, audible at some distance from the chest, whose heart was hypertrophied and presented a cribriform condition of the aortic valve, and one-quarter inch below it in the left ventricle three other rudimentary cusps.

In one of Babes' cases of bicuspid aortic valves, a peculiar band, like a papillary muscle of the mitral valve, traversed the sinus of valsalva. Hektoen[2] quotes from the literature several other instances of anomalous cords at the level of the valves, and a case observed by himself of a large defect at the base of one of the segments, all of which he ascribed to defects in the development of the aortic septum.

Defective Development of the Semilunar Cusps.—In a few instances of bicuspid valve a gap may be left on the wall of the vessel between the segments where evidently no third cusp has formed. This occurred in 2 cases of Deteindre's series. A remarkable instance of such a defect in the pulmonary valve is recorded by Stinzing.[3] Here there were only two pulmonary cusps, and a large free space occupying the position of the third was traversed by two low ridges, evidently its rudiments. The right heart was greatly hypertrophied and dilated, the left ventricle appearing as a mere appendage to the right. It was from a woman, aged sixty-four years, presenting signs and symptoms of pulmonary insufficiency, a history of pneumonia eight months before death, and failing compensation since. It was thought that the free space had been present since birth, but that the other two cusps had sufficed to close it in, until the rise of pressure in the right heart, developing in the pneumonia, led to dilatation of the pulmonary artery, and thus to the pulmonary insufficiency.

PRIMARY DEFECTS OF THE AURICULO-VENTRICULAR ORIFICES.

Congenital disease of the auriculo-ventricular valves differs from that of postnatal life chiefly in its infrequency, in the more extreme character of the process, atresia being more common than stenosis, and in the fact that the right side of the heart is usually affected rather than the left. Owing to the rarity of the cases, to the short duration of life, and to the fact that in the infant heart the picture presented is hard to distinguish from that of the more frequent lesions at the arterial ostia, this subject is not of great clinical importance, and its chief interest may be said to lie in the contribution which it brings to our information upon the vexed question of the pathogenesis of cardiac defects.

[1] *Dublin Hospital Gazette*, 1857, p. 33. [2] *Chicago Pathological Society*, 1905.
[3] *Deut. Arch. f. klin. Med.*, March 14, 1888.

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Tricuspid Stenosis and Atresia.—Congenital Tricuspid Stenosis.—Although this lesion is not very uncommon in adults, the cases which can be proven to have originated in intra-uterine life are very rare. Rauchfuss knew of only two instances of primary congenital tricuspid stenosis unassociated with pulmonary disease—namely, Peacock's and Romberg's cases. To these Vierordt adds another from Kucher.

Under the title "Congenital Tricuspid Stenosis," Stow[1] reports a woman aged twenty-eight years, without any history of previous illness except measles at the age of six years, presenting physical signs of mitral stenosis and relative tricuspid insufficiency with symptoms of failing compensation and moderate cyanosis coming on six months before death, in whose heart the tricuspid segments were united into a thin diaphragm "showing no sign of past or present inflammation," and having a hole in its centre 1.5 cm. in diameter. The mitral cusps were thickened, calcified, fused, and the orifice much constricted.

In combination with pulmonary stenosis or atresia, congenital tricuspid stenosis is somewhat less rare. In the heart of an infant aged four months, with cyanosis from birth, presented to the McGill Museum by Dr. Osler, the pulmonary cusps are thickened and fused, and the orifice much stenosed; the tricuspid segments are likewise thickened and fused, and carry recent vegetations, their chordæ are short, thick pillars, and the tricuspid orifice admits the tip of the little finger; the ventricular septum is entire, the foramen ovale patent, and the right auricle enormously dilated. Such cases are undoubtedly of inflammatory origin, and are of great value as proving that, although the importance of fœtal endocarditis as a cause has probably been much over-rated, it has its place as an etiological factor in congenital cardiac disease.

Tricuspid Atresia.—Tricuspid atresia, in which the orifice is obliterated, although itself infrequent, is the commonest of all congenital lesions of the auriculo-ventricular valves. Rauchfuss enumerates from the literature 16 cases of primary tricuspid atresia in which the pulmonary artery was either of normal size or dilated, and Vierordt quotes one other from Chapotot. To these may be added Bernstein's case, in which, with no trace of tricuspid orifice or valve, the interauricular septum was absent except for a small strand, the interventricular septum defective at the base, the right ventricle rudimentary with a very small cavity and a large dilated conus, and there was an irregularity in the origin of the branches from the aortic arch.

This case is descriptive of the main findings in primary tricuspid atresia. The orifice is either entirely absent or is represented by a cicatrix, the right auricle and left ventricle are greatly enlarged, the right ventricle is aplasic, and a patent foramen ovale or defect of the interauricular is combined with a defect of the interventricular septum, the course of the circulation being from the right to the left auricle, thence to the left ventricle, and through the defect in the septum into the conus of the pulmonary artery.

Etiology.—Tricuspid atresia may be explained either as the result of a fœtal endocarditis or as a primary defect in development.

(*a*) *Fœtal Endocarditis.*—In spite of the fact that a secondary endocarditis is prone to supervene at the seat of a valvular anomaly, and that its action as a

[1] *American Journal of the Medical Sciences*, August, 1905

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primary cause is therefore difficult to prove, certain points indicate that some cases of tricuspid atresia have an inflammatory origin. There can be no doubt that some instances of congenital stenosis which present identical appearances with the stenosis of chronic valvular disease of adult life are due to an antenatal valvulitis, and it is reasonable to suppose that in some instances in which a defect of the septum and a patent foramen ovale, through which the circulation can be carried on, co-exist, such a stenosis may progress to complete atresia. Rauchfuss remarks that where the defect in the interventricular septum is very small, as in Ferber's case of a girl aged five years, the tricuspid atresia must have been only recent, and have developed through a stenosis as the result of a progressive inflammation. He points out further that a widespread thickening and contraction of the lining of the ventricle and of the pulmonary valve indicates such an origin, and suggests that the endocarditis may begin about the margins of the septal defect and spread thence to the neighboring tricuspid valve.

(*b*) *Defect in Development.*—The majority of the cases of primary tricuspid atresia may be assumed to have their origin in a defect in development. It is hard to imagine an endocarditis localized to so tiny an area as this must have been before the closure of the septum occurred. Again, he fact that congenital stenosis, which would represent an earlier stage of an inflammatory process, is rarer than is atresia, indicates that such an origin is unusual. A further very strong argument in favor of a developmental origin is that these cases are nearly all associated with grave anomalies elsewhere in the body or in the heart itself. It will be remembered that in the development of the heart the auriculo-ventricular orifice is at first single, lying in the left side of the common ventricle, and that it becomes divided into the tricuspid and mitral ostia by the development of endocardial cushions in its centre. These may entirely fail to form, in which case a common ostium surrounded by five cusps will result. Again, should these cushions be deviated too far to the right or left in their development, they may become adherent to the corresponding wall of the common ostium, or, at least, the orifice on that side will be reduced in size, and a tricuspid atresia or stenosis of developmental origin will result. This is Rokitansky's explanation of his case of mitral atresia.

Rauchfuss classifies the 16 cases he collected as (*a*) due to a defect in development (where there is no trace of a tricuspid orifice—Kreysig, Valleix, Nuhn, Vrolik, and Peacock); (*b*) as of inflammatory origin (Burdach, Schuberg, Henriette, Ferber, Barlow), and the remainder as "doubtful." Vierordt follows the same division.

Symptomatology of Tricuspid Stenosis and Atresia.—Cyanosis may be present at birth, or may first develop after a few days or weeks. In Bernstein's patient, aged two years and eight months, it did not appear until the sixteenth month, but then became marked with clubbing, and a polycythæmia of 10,000,000 developed. This late appearance was possibly explained by the absence in this case of the auricular septum, a condition which must have facilitated the circulation. On the other hand, Kelley's patient, a delicate, unhealthy looking child, showed only slight lividity on crying or when he had a cold, and in Sieveking's case, dying at nine weeks, cyanosis was absent throughout, but dyspnœa was a prominent symptom.

Peacock uses his case of marked cyanosis in tricuspid stenosis with closed foramen ovale as an argument that cyanosis is not dependent upon the

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mixture of venous with arterial blood, but upon venous congestion, for the defects present in the interventricular septum were larger on the side of the left ventricle, showing that the current through these had passed from left to right.

Physical signs in tricuspid atresia are not characteristic, being obscured by those of the septal defect that is always present, and by the fact that a murmur with its maximum intensity over the right ventricle may be confused with one from the pulmonary area; or murmurs may be entirely absent, as in Moore's case. The marked hypertrophy of the left and the small size of the right ventricle might serve to distinguish tricuspid from pulmonary disease, but here again increased dulness from the enlarged right auricle might be misleading. In tricuspid stenosis the physical signs may be those of the insufficiency usually associated.

Duration of Life.—The majority of patients with tricuspid atresia die within the first year of life. Bernstein's reached two years and eight months, and this relatively high age is perhaps explained by the absence of the interauricular septum. In rare instances, as in Burdach's, dying in the twenty-eighth year, adult life is attained, but here it is probable that the condition began as a stenosis, and that atresia had developed later.

Mitral Stenosis and Atresia.—Congenital Mitral Stenosis.—Congenital mitral stenosis is even rarer than the same lesion at the tricuspid orifice. A typical case, evidently due to an antenatal valvulitis, in a child with cyanosis and dyspnœa from birth and characteristic physical signs, dying suddenly at nineteen months, is reported by Simmons. Vierordt says that isolated mitral stenosis due to a primary defect of development had not, to his knowledge, yet been recorded.

Mitral Atresia.—A complete obliteration of the mitral orifice is also very rare. The same remarks apply in regard to etiology as in the case of tricuspid atresia, but here a primary defect in development (as a deviation to the left of the primitive endocardial cushions in the common auriculoventricular orifice) may be usually assumed. In Thérémin's one hundred and sixth observation of an infant aged two days, the left auricle and ventricle were aplasic without any trace in the latter of a mitral orifice, its walls being formed throughout of finely reticulated muscle fibres; the foramen ovale was closed, the interventricular septum defective, the pulmonary valve bicuspid, and the aorta appeared to arise from the right ventricle; there was a *horseshoe kidney and double ureter*. Lawrence and Nabarro[1] give a similar case of mitral atresia, defect of the septum, aplasic left ventricle, the aorta arising behind the pulmonary artery from the right ventricle, with *coarctation of the aorta, transposition of the stomach, absence of spleen and hepatic section of inferior vena cava; anomalies in form of liver and lungs.* In Rokitansky's case of aortic and mitral atresia with defect of the septum, patent foramen ovale, and dilated pulmonary artery, in a child aged twelve days, there was an *accessory right bronchus.*

These grave associated anomalies, which are present also in most of the few other cases recorded, argue strongly for a developmental origin of mitral atresia.

Congenital Tricuspid Insufficiency.—Congenital tricuspid insufficiency may result from a primary malformation of the cusps or of their

[1] *Journal Anatomy and Physiology*, 1901-02, p. 62.

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papillary muscles, or from secondary deformity in the arrest of development of neighboring structures. It may be due to thickening and shortening of the valve in a fœtal endocarditis; thus Barth and Roger describe a case in which, on auscultation before birth, a long, loud, rough murmur was heard accompanying the fœtal heart sounds. The child was stillborn three days later, and the right ventricle was found dilated, the tricuspid orifice enlarged, and its cusps shrunken, insufficient, and evidently the seat of an endocarditis. In the case of Steffen, of a boy aged ten and a half months, with hypertrophy and dilatation of the left ventricle and dilatation of the right, there were no tricuspid segments, but the valve formed a low ridge which was thickened, reddened, and slightly jagged. The mitral cusps were similarly thickened and reddened, and one of them was reduced likewise to a narrow ridge, and the chordæ tendineæ were much shortened, while the foramen ovale and ductus were closed. Thus there existed here a tricuspid and mitral insufficiency which apparently originated in the last weeks of fœtal life.

Congenital Mitral Insufficiency.—Steffen's case is the only instance found in the literature. True congenital tricuspid insufficiency is also rare, probably not a dozen cases (including primary malformations as well as those due to fœtal endocarditis) being recorded.

The physical signs and general results of congenital tricuspid and mitral insufficiency, as well as of mitral stenosis, are similar to those of the same lesions in the chronic valvular disease of later life.

ANOMALIES OF THE AURICULO-VENTRICULAR CUSPS.

Double Auriculo-ventricular Orifice.—A second smaller opening, furnished with its own cusps, chordæ tendineæ, and papillary muscles, may lie in the body of one of the segments of an otherwise perfectly normal mitral or tricuspid valve. Three such cases are recorded, 2 of double mitral orifice by Greenfield[1] and Cohn,[2] and 1 of double tricuspid by Pisenti.[3] A fourth case, not previously reported, is in the McGill Museum (Fig. 42). It is apparently unique, in that a double mitral orifice is associated with a defect of the lower part of the interauricular septum and with resulting deformities of the auriculo-ventricular cusps, which may possibly give a clue to its origin.

The heart is from a child aged five years; it is of bizarre form, with a bifid apex and a very deep auriculo-ventricular groove, below which the greatly hypertrophied pulmonary conus projects prominently to the right, while the aorta and pulmonary artery, somewhat twisted on their axes, arise from the extreme left angle of its base. The right auricle and ventricle are hypertrophied and dilated, and are larger than the left. The interauricular septum is displaced to the left, and in its upper and posterior part is a valvular patent foramen ovale. Its lower two-thirds is absent, a large crescentic defect (*persistent ostium primum*) existing, the lower border of which is formed by projecting cushions sent upward from the left auriculo-ventricular valve

[1] *Transactions Pathological Society*, London, 1876, xxvii, p. 128 (with plate).
[2] *Inaugural Dissertation*, Königsberg, 1896 (with plate).
[3] *Di una rarissima Anomalia della tricuspide*, Perugia, 1888.

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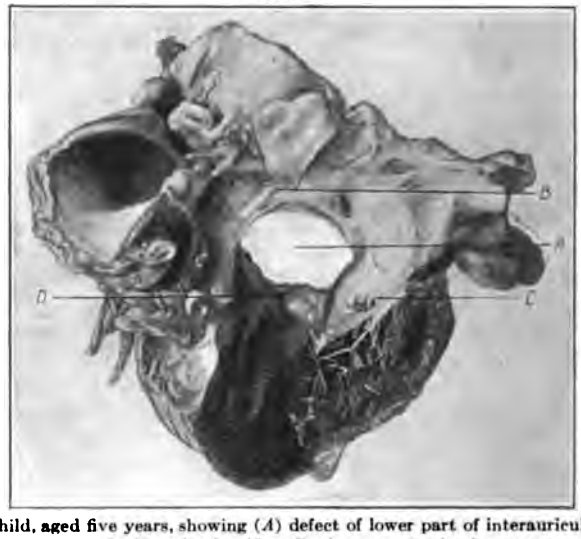
at its insertion along the base of the interventricular septum. The right auriculo-ventricular orifice is very large, the left about normal in size. The mitral valve is replaced by one large segment which arises by slender chordæ from a single group of papillary muscles and passes forward on either side into the middle point of the base of the interauricular septum, where this forms the lower border of the large defect in the auricular septum. The secondary mitral ostium lies in the posterior half of this large primary segment, about 7 mm. back from its free margin, and some 2 cm. behind its insertion into the middle of the base of the interventricular septum. It appeared at first as an oval cleft in the valve, but on inspection revealed itself as a perfect valvular opening, its long diameter parallel to that of the primary mitral ostium, of a calibre admitting a large lead-pencil, and furnished with two perfect cusps of which the posterior is the larger. These cusps are

FIG. 42



Heart of a child, aged five years, showing (*A*) defect of lower part of interauricular septum; *B*, patent foramen ovale; *C*, double mitral orifice; *D*, cleavage of mitral segment. (From a specimen in the Pathological Museum, McGill University.)

attached to slender chordæ which arise in two groups from two short papillary muscles, which lie behind and are quite independent of the single group from which the chordæ of the primary mitral segment spring. The right auriculo-ventricular valve is irregularly formed. A large gap, 3 cm. long, exists between the septal and infundibular cusps, and an accessory cusp intervenes between the latter and the marginal segments. The septal cusp is very irregular and has a jagged excavation along its left border, which simulates, but proves not to be, a double tricuspid ostium. The aortic valve has two semilunar cusps of equal length, behind one of which arise the two coronaries separated by a low raphe. All the valves are thin and healthy.

Etiology.—Pisenti explained the condition as the result of a congenital fenestration which had transmitted the blood stream in early embryonic

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life, and thought that its transformation into a second valvular orifice was an adaptation of growth or compensatory process, the papillary muscles (which are known to develop at about the same time as the cusps) growing up with their chordæ to its borders. Cohn dismisses this theory as unsatisfactory, saying that the anomaly does not represent any known stage of embryonic development, and that its origin is entirely obscure; he suggests that it may be simply a development by excess.

The arrangement of the papillary muscles in our specimen, as well as in that described by Cohn, suggests strongly that the double orifice is in some way associated with their anomalous origin, as in Pisenti's theory.

Symptoms.—None of the patients showed any symptoms during life, and Cohn's attained the age of seventy-one years. The primary segments were normal in all and the secondary cusps were evidently competent and functioned also as valves. The double orifice is thus of no clinical significance.

Another form of "double mitral orifice" is described by Andrewes,[1] in which two orifices separated by a fibrous septum lay one behind the other in the left ventricle; the right ventricle was rudimentary, the size of a pea, and the tricuspid valve absent. The foramen ovale was widely patent and the ventricular septum defective. This is explained by the author as a deflection of the interventricular septum to the right, so that both orifices come to lie in the left ventricle.

Miscellaneous Anomalies.—Various minor defects, as irregularly formed or accessory leaflets, anomalous arrangement of the chordæ tendineæ, anomalous papillary muscles, etc., occasionally occur. They are of no clinical importance except in so far as they may in some instances contribute to an insufficiency of the valves. In the more serious defects, the tricuspid valve is the one always involved in all the recorded cases.

PATENCY AND ANOMALIES OF THE DUCTUS ARTERIOSUS BOTALLI.

The ductus arteriosus of the fœtus is a short, thick trunk, 10 to 15 mm. long, running from the left branch of the pulmonary artery directly after the bifurcation to the under side of the arch of the aorta just beyond the origin of the left subclavian artery, and serves to carry the unaërated blood, returned from the head and upper extremities, to the descending aorta, whence it passes to the placenta. At birth the ductus is thrown out of use and undergoes a rapid involution, its lumen becomes practically impermeable about the third week of life, and the alterations in its wall, which lead to its permanent obliteration, go on for some months, and finally transform it into the ligamentum arteriosum of later life. The average diameter of the patent ductus at birth is given by Vierordt at 5 to 6.8 mm. and by Thérémin as 4.8 mm. But when filled with fluid during life, or experimentally injected directly after death, it is found to be much larger, approximating in circumference to that of the adult common carotid artery. Thus in a series of infant hearts prepared by Klotz, in which he injected the ductus from the aorta with gelatin at autopsy, it was found in the newly born to be fully equal in size to the main pulmonary

[1] *Transactions Pathological Society*, London, 1903, liv.

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trunk. He explains its apparent relative smallness as usually seen postmortem by a firm contraction of the muscular vessel wall.

The existence of this canal and its obliteration after birth was already known to Galen. Its anatomical relations and place in the fœtal circulation were accurately described by Harvey (1628), to whom also its occasional patency was familiar. An historical account of the earlier writers upon it will be found in an article by Strassman.[1]

The ductus may (1) remain patent throughout life and (2) undergo aneurismal dilatation; (3) it may be absent, or (4) it may have an anomalous origin or course.

Patency of the ductus is not infrequent in combination with other cardiac defects, especially those in whom there is some serious interference with the pulmonary circulation. It occurred in 106 of this series of cases, in 15 of which it was combined with pulmonary atresia, in 7 with pulmonary stenosis, and in 19 with transposition of the great trunks. As an isolated condition it is among the more infrequent of cardiac anomalies. Vierordt knew of only 26 cases with postmortem findings in the literature, to which may be added those of Drasche,[2] Simmons,[3] Libman,[4] Bommer,[5] who gives one of his own and 3 cases quoted from *Schmidt's Jahrbuch*, Gibson,[6] Roeder, Wagener[7] (3 cases), Voss[8] (aneurism), and Gruner[9] (aneurism). The remarks in this section will of course apply chiefly to such cases of primary patency.

Pathogenesis.—The causes of patency of the duct are to be sought in the conditions of its normal closure, and this must depend upon the influences, mechanical or otherwise, of the changes in the circulation at birth and upon the action of the vessel wall, itself a fœtal structure destined to involution.

As *possible factors* in the process of closure may be enumerated (1) peculiarities in the histological structure of the ductus wall, (2) alterations in the blood pressure at birth, (3) modifications at birth in the position of the ductus relative to the aorta and pulmonary artery.

1. **Histology.**—The ductus wall is poor in elastic tissue as compared with the aorta and pulmonary artery, but is relatively rich in muscular elements (Langer, Walkhoff, Thoma,[10] Kautsch,[11] Klotz[12]). More particularly a loose, subintimal layer of muscle is present (Thoma); this evidently corresponds to Jore's musculo-elastic layer of the arterial wall, which is here developed both at an earlier period and to a greater extent than in the aorta and pulmonary artery. It is especially marked at either extremity of the duct where it can be seen to pass into and, indeed, to form the musculo-elastic layer of the aorta (Klotz). In view of the unanimity upon this point of the observations of so many workers, the contrary statement of Pfeiffer,[13] that in

[1] *Archiv f. Gynäk.*, 1894, Bd. 45.
[2] *Berlin. klin. Woch.*, 1898, p. 1195.
[3] *Intercolonial Medical Journal of Australasia*, February 20, 1906.
[4] *Transactions Pathological Society*, London, May, 1905.
[5] *Freiburg Thesis*, 1900.
[6] *Edinburgh Medical Journal*, 1900.
[7] *Deutsch. Arch. f. klin. Med.*, 1904, lxxix, p. 90.
[8] *Kiel Thesis*, 1900.
[9] *Freiburg Thesis*, 1904.
[10] *Virchow's Archiv*, 1883, Band xciii.
[11] *Halle Diss.*, 1896 (quoted by Gruner).
[12] *Transactions Association of American Physicians*, 1907.
[13] *Virchow's Archiv*, Band clxvii.

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the ductus arteriosus the elastic tissue is especially developed while the muscular elements are scanty, may be dismissed.

2. **Alterations in the Blood Pressure at Birth.**—Previous to birth the pressure is highest in the right side of the heart; the pulmonary arteries are small, and almost all the blood passes though the ductus into the aorta. At birth the lungs are expanded, their capillaries are opened, and there is an immediate lowering of pulmonary blood pressure. Landau supposed an active aspiration of blood into the pulmonary artery with the first breath, and a resultant negative pressure in and collapse of the ductus. Against this view is the evidence that the closure is not necessarily immediate. Schultze thought that after birth a marked fall of pressure in the pulmonary artery occurs, and that complete closure takes place at that moment when the pressure in the aorta becomes equal to that in the pulmonary, so that the blood in the ductus stagnates, and that this event may take place immediately, or some days after birth, and that closure is made permanent by an annular contraction of the ductus. Klotz ascribes closure to two factors, the alteration in the pulmonary pressure and the rich muscular structure of the wall. Dr. Adami suggests to the writer that a consideration of the circulatory conditions indicates that for some little time after birth the work the heart is called upon to perform, and therefore the mean arterial pressure, is lowered as compared with what it was antepartum, and in this lowering is to be found a main factor in the contraction and obliteration of the ductus.

3. **Alterations in the Position of the Ductus Relatively to the Great Vessels.**—Schantz supposed a stretching of the duct by the movement of the pericardium, pulmonary artery, displaced thoracic organs, and sternum, in the initial respiration, Walkhoff a bending of the duct upon itself and a consequent slowing of the stream leading to thrombosis with subsequent organization. Strassmann describes, on the basis of a large number of injection experiments, a fold in the aortic wall in the upper border of the mouth of the duct, which he thinks closes its opening in a valvular manner when the pressure rises in the aorta at birth. The constancy of this fold has been disputed by later observers, notably Sharpe, and the fact that in Wagener's three cases of patency it was markedly developed, yet closure did not occur, argues against its efficiency.

Process of Closure.—A discussion of the part which the different factors may play in the closure may be preceded by a statement of the actual observations that have been made upon the process itself. In a number of the cases of patency in infants a wrinkling of the lining is noted, evidently in beginning obliteration. Ridlei (quoted by Strassmann) mentioned this appearance as long ago as 1738. The obliterating process is described as beginning at the middle of the duct and progressing first toward the pulmonary and then toward the aortic end (Langer). Klotz finds the contracture most marked at either end, and this view is supported by the bean-shaped form of the duct seen in the so-called aneurisms.

The Part Played in Closure by the Various Factors.—The blood pressure in the ductus is evidently important. Thus, if the pulmonary pressure keeps up, as in atelectasis of the lungs, the ductus remains patent. Patency also exists in most cases of pulmonary atresia (where there is low pulmonary pressure), and in aortic atresia (where there is low aortic pressure). The muscular structure of the wall undoubtedly is peculiarly strongly developed, but if the mean pressure in the ductus remains the same after as before

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birth (and this whether the current now passes from the aorta or from the pulmonary artery), muscular tone cannot alone bring about obliteration of the canal. It can only do this provided the pressure after birth is diminished as compared with what it was before. This seems to be probably the case, judging from the comparative size of the left and right ventricle at birth, some considerable time intervening before the mass of the left ventricle, postpartum, equals in size that of the right ventricle immediately antepartum. Again, before birth the heart as a whole has to exert sufficient force to keep up the placental circulation, and at birth this labor is cut off. Both the size of the infantile lungs and the relationships of the circulation at this time compare favorably in the matter of cardiac work with the size of the placenta and the effort to maintain its distant circulation.

These general considerations seem to lead to the conclusion that in the days immediately following birth there is a lowered pressure in the ductus arteriosus, and if prior to birth the pulmonary pressure kept the ductus patent, despite its strong musculature, the lowering, postpartum, both of the pulmonary and of the aortic blood pressure, and so of that in the ductus, will permit its muscular wall to contract and to obliterate the canal.

A mechanical cause for closure, such as a modification of position leading to kinking or stretching of the duct (Schantz), cannot be said to be proven, and such a theory would seem to leave out of account the force required to produce such a change in as large a vessel as the ductus arteriosus (Klotz). Thrombosis (Walkhoff) is no longer considered to take any part in normal closure.

Thus the two main factors in the normal obliteration of the duct appear to be (1) the lowering of the mean blood pressure after birth, and (2) the relative muscularity of the wall of the ductus arteriosus. It follows that we must ascribe continued patency of the duct in the main to deficiency of one or both of these factors; that is, it will occur in conditions in which the blood pressure, either in the pulmonary artery or the aorta, is maintained at a level approximating to that before birth (as in atelectasis of the lungs), or in those in which a congenital defect in the structure of the ductus wall exists. That such a defect is not uncommonly the cause of patency is suggested by the frequent association of anomalies elsewhere in the body and by the not uncommon occurrence of a history of syphilis, or of anomalies in other members of the same generation, as in De la Camp's remarkable series[1] of six brothers and sisters all with characteristic physical signs of patent duct which was diagnosed by the *x*-rays.

Pathology.—Two principal types of patency may be distinguished: (1) In rare cases the duct may be greatly shortened upon itself so that its ends are approximated to each other, and it disappears as a canal, remaining as a simple aperture between the two great trunks. Such was Drasche's case, where in a woman aged twenty-nine years, a circular opening 3 cm. in diameter, with lipped borders, lay at the situation of the duct and formed a direct communication between the aorta and pulmonary artery, "which touched each other here;" so also in Babington's, in which there was coarctation of the aorta just beyond the left subclavian, and immediately beyond this again a circular opening larger than a goose-quill leading directly into the pulmonary artery, the remains of the ductus arteriosus.

[1] *Berliner klin. Woch.*, January 19, 1903.

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(2) More frequently the ductus persists as a short canal from 0.4 to 2 cm. long (Vierordt), with a lumen varying in size from one just admitting a bristle to one allowing the passage of a "goose-quill," "pencil," or even, as in Luy's case, the "finger." Gerhardt states that a patent ductus of long standing is usually shorter and broader than the fœtal vessel. In form this canal may be (*a*) cylindrical, as in Fagge's[1] case, admitting a No. 6 catheter, or (*b*) funnel-shaped (*i. e.*, pyramidal, as in a funnel without a stem), with its larger end toward the aorta, as in a case by Murray,[2] where, in a woman aged thirty-six years, it formed a truncated cone three-eighths of an inch long, just admitting a quill, and lying with its base to the aorta; and another by Walsham,[3] in a man aged forty-seven years, where a canal one-half inch long and one-quarter inch wide at its aortic end was contracted at the pulmonary to admit a No. 4 catheter. Finally (following Gerhardt's classification into four types, of which the above forms 1, 2*a* and *b* constitute the first three), the patent duct may exist (3) as a canal which has undergone aneurismal dilatation.

In a patent ductus with otherwise normal conditions, the blood stream will be directed chiefly from the aorta, where the blood pressure is highest, into the pulmonary artery. This is evidenced by the funnel-shaped form with its base toward the aorta, which the canal often assumes, and by the occasional presence of mycotic vegetations on the adjacent or opposite wall of the pulmonary artery (Murray's case). Wagener's 3 cases, in which the membrane at the pulmonary end bulged into the artery, also indicate this direction of the stream. Where aortic stenosis is present the current will, of course, be reversed. Dilatation of the pulmonary artery, and hypertrophy and dilatation of the right ventricle, are usual results of patency of long standing. Rokitansky, Gerhardt, and Rauchfuss thought them characteristic of all cases, but exceptions occur. The left ventricle may share in the hypertrophy and the aorta be moderately dilated. In Fagge's case, a woman aged forty-two years, the heart weighed twenty-three ounces; the right ventricle was greatly hypertrophied, being equal to the left in thickness; the tricuspid orifice admitted six fingers, the right auricle was dilated, and the main pulmonary branches, especially the right, were much dilated. The left ventricle is occasionally hypertrophied in excess of the right, as in Murray's and Kidd's[4] cases, aged respectively thirty-six and twenty-two years. In rare instances, as in Walsham's and Drasche's cases, aged respectively forty-seven and twenty-nine years, the heart may not be hypertrophied at all.

Arteriosclerotic patches are not uncommon in the neighborhood of the patent duct in the aorta, and occur, although less frequently, in the pulmonary artery. In Hebb's remarkable case the atheroma and dilatation of this trunk seem to be explained rather by the obliteration of its left branch through the pressure of the thrombosed duct.

Vegetations of a malignant character in the course of an acute endocarditis are not uncommon within a patent duct, about its aortic orifice, or on the adjacent wall of the pulmonary artery (Wagener, Kidd, Murray). Thrombosis of its lumen may occur as a result of infective embolism (Buhl), or

[1] *Guy's Hospital Reports*, 1898, p. 1195.
[2] *Transactions Pathological Society*, London, 1888, xxxix, p. 67.
[3] *Ibid.*, 1876, xxviii, p. 43.
[4] *Ibid.*, 1892, xliv, p. 47.

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of localized disease of the wall (Gruner), or of stagnation of the stream from kinking of the duct and other causes.

Symptoms.—Clinical evidence of patency of the duct is to be sought rather in physical signs than in symptoms, which are often obscure. The typical appearance is one of anæmia, sometimes profound, which has been described as wax-like. Cyanosis is usually absent; when present it is generally slight and transient, appearing only on exertion, and usually develops late, sometimes as a terminal event (Schnitzler, Kaulich). Of the 19 cases in which this point is mentioned, cyanosis was entirely absent in 13, of which 8 were in adults (Murray, Kidd, Walsham, Fagge, Drasche, Wagener), 3 in children (Arnheim, Müller, Bommer—Case 2), and 2 in infancy (Libman, Rees). Cyanosis was noted as slight in 3 cases, in one of which, namely, Bittorf's (aged eleven years), it was constant, in the others transient, appearing only on crying in Simmons' (aged sixteen weeks), and during anginal attacks in Hale White's[1] case (aged fifty-three years). It was marked in 3 cases only, in 2 of which, those of Almagro[2] and Carmichael,[3] it was persistent and came on late, in the former (dying at nineteen) in the third year, in the latter (dying at three) soon after birth, becoming extreme, with clubbing and a polycythæmia of 8,100,000. In both these cases coarctation of the aorta was associated with the patent duct, and in that of Carmichael mitral stenosis with great dilatation of the left auricle was present as well, suggesting a rise of pressure in the pulmonary artery and a possible reversal of flow, venous blood from this vessel entering the aorta through the canal. In Bommer's case (aged sixteen weeks) the cyanosis was transient, present only during dyspnœic attacks, which came on especially during feeding, and recurred at last so frequently that the child failed for lack of nourishment; during the attacks the breathing stopped suddenly and deep cyanosis developed, lasting two to four minutes; it passed off entirely as the breath returned, in the interval the color being normal. This again is very suggestive of an admixture of venous with arterial blood as the cause of the temporary cyanosis, the pressure becoming higher in the pulmonary artery and lower in the aorta during the act of sucking.

Considering the otherwise mild character of the symptoms, cardiac seizures of various sorts are relatively common. Typical dyspnœic attacks occurred in the cases of Almagro, Carmichael, and Bommer, quoted above, and in that of Sanders (quoted by Vierordt). Paroxysms of extreme tachycardia (pulse 200), with dyspnœa and bloody expectoration, lasting for some hours and recurring every few months, are described in a man aged thirty-six years, with dyspnœa and palpitation on exertion for years, but no cyanosis (Bommer).[4] Hale White reports repeated angina-like attacks, in one of which death occurred, in a man aged fifty-three years, with a patent duct the size of the anterior tibial artery, but no hypertrophy of the heart or disease of this or of the aorta.

Epistaxis, hæmatemesis, and hemorrhages from other mucous surfaces are not uncommon (Almagro, Carmichael), as is also dyspnœa. Unless death occur from some intercurrent condition, the patients usually die with failing compensation.

[1] *Transactions Pathological Society*, London, 1885, vol. xxxvi, p. 182.
[2] *Schmidt's Jahrb.*, Bd. cxv, p. 140 (quoted by Bonner).
[3] *Edinburgh Hospital Reports*, xi, p. 229. [4] *Schmidt's Jahrb.*, Bd. 164, p. 142.

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Physical Signs.—These are almost invariably present and are often characteristic. Since the work of Gerhardt, François Franck, and others, a number of clinical observations have been published. The cases confirmed by autopsy are still, however, relatively few. Among 19 cases with histories attached (in which are included 3 cases by Bittorf, Arnheim, Müller, with characteristic physical signs and *x*-ray diagnosis, but not confirmed postmortem) physical signs were absent in only two instances, in both of which marked cyanosis was present. In one of these (Bommer) the heart sounds were clear and the cardiac dulness normal; in the other (Carmichael) there was precordial bulging and an impure first sound at the apex, explained by the mitral stenosis present. Absence of physical signs in the case of Walsham, quoted by Vierordt in this connection, must be pronounced doubtful, for the specimen came from the dissecting-room with an indefinite note that cyanosis and pericardial murmurs existed. A negative finding in the cases by Luys and Duroziez was also disputed by Almagro.

The distinctive physical signs as well as the absence or late appearance of cyanosis depend, as Gerhardt pointed out, on the fact that a patent duct of long standing usually has a short, wide lumen through which during systole blood flows freely *from* the aorta into the pulmonary artery, which dilates accordingly and becomes, with the ductus itself, the chief seat of whatever vibration or murmur the abnormal current may produce; the right ventricle behind it usually undergoes hypertrophy and dilatation as well. Gerhardt described as characteristic a visible systolic pulsation in the second left interspace (indicating the forcible closure of the pulmonary valves), an increased area of cardiac dulness, especially to the right, and a narrow zone of dulness 3 to 4 cm. wide (corresponding, he believed, to the dilated pulmonary artery) lying at the base of the heart, along the left sternal border from the third to the second or first rib, and extending a little way over the first piece of the sternum. This "ribbon-shaped" dulness was disputed by some; it was absent in Drasche's case (in which, however, there was no cardiac hypertrophy or pulmonary dilatation noted postmortem), and Skoda found no change of tone over the dilated pulmonary. It has been noted, however, by many other observers, and has recently been strikingly confirmed in a number of cases published by Zinn, Arnheim, Bittorf, De la Camp, Müller, and others, in which Gerhardt's dull area, with characteristic murmur or thrill localized over it, has been found to correspond with a pulsating shadow lying above the base of the heart, which was evidently from its size and position the dilated pulmonary artery. In Bittorf's case this shadow was seen, when looked at from the side, to be the size of a walnut and to pulsate a little later than the heart and synchronously with the aorta. In Arnheim's[1] the *x*-rays showed, besides enormous hypertrophy of both sides of the heart, which occupied nearly the whole left thorax, the greatly enlarged shadow of the pulmonary artery placed above the cardiac shadow "like a cap," and numerous tortuous dilated vessels, indicating an extensive collateral circulation and a probable co-existing coarctation of the aorta.

Where cardiac hypertrophy is marked, precordial bulging, diffuse pulsation, and other evidences will be present. An increased area of cardiac dulness, especially to the right, while usual, is not invariable (as was stated

[1] *Berl. klin. Woch.*, July, 1903, p. 616.

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by Rokitansky and Gerhardt), for the left ventricle may be hypertrophid in excess of the right (Murray's case), or in rare instances there may be no cardiac hypertrophy at all (Drasche's case), and the area of cardiac dulness will of course correspond.

A *thrill*, usually systolic, but sometimes continuous through the cardiac cycle, is fairly frequent, and was present in 7 of the 19 cases. It may be diffuse over the precordium, but is usually localized to the neighborhood of the second left interspace, in the region described above as Gerhardt's dull area, or at least is of maximum intensity here. Its transmission obliquely upward below the clavicle (along the course of the pulmonary artery) is said to be pathognomonic.

The auscultatory phenomena are the most important and constant. A loud murmur is nearly always produced, which is characterized by almost all observers as peculiar, and is variously described as harsh, musical, scraping, scratching, humming, churning, rushing, rolling, and only rarely as blowing. Müller compares it in his case to "rolling thunder," and says that two different listeners likened it independently to the noise made by a train in passing through a tunnel. In rhythm several different types may be made out: (1) The murmur is frequently systolic (as in the cases by Murray, Hale White, Simmons, and Bittorf). (2) It may begin with systole, but continue into and through diastole, either as a continuous hum (Libman's case), or with a systolic rise (Bommer), or with a rhythmic, systolic, and diastolic accentuation (Müller). Gibson[1] describes as pathognomonic a continuous, rushing murmur which "begins distinctly after the first sound, accompanies the latter part of that sound, occupies the first pause, accompanies the second sound (which may be accentuated in the pulmonary area, or doubled), and finally dies away during the long pause." (3) Sometimes, as in Drasche's case, two independent murmurs are heard at the pulmonary area, the loud, peculiar, systolic one, and a low, short, diastolic, indicating a slight regurgitation into the aorta during the pause. (4) Very rarely the murmur is diastolic in rhythm, as in Fagge's case, where a diastolic murmur, musical and of a wavy character, was localized to the pulmonary cartilage. The point of maximum intensity is usually in the second or third left interspace, and it is often heard very loudly in the first left interspace below the clavicle and over the first part of the sternum and in the back to the left of the third and fourth dorsal vertebræ, and in the left suprascapular region (François Franck). It is transmitted over the left ventricle, and its systolic element often is audible over the carotids, sometimes more distinctly over the left than over the right (Arnheim, Gerhardt). It is said not to be transmitted over the right ventricle, and Müller describes it in his case as diminishing abruptly below the third left costal cartilage.

François Franck and other French writers mention, as of diagnostic value, an inspiratory accentuation and an expiratory diminution both of the characteristic murmur and of the radial pulse (pulsus paradoxus), which they explain by saying that during inspiration the pressure in the thorax is lowered, so that more blood can enter the pulmonary artery then than during expiration, and this will lead to a smaller pulse wave from the aorta,

[1] *Medical Press and Circular*, May 30, 1906.

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to a larger current through the canal, and a correspondingly louder murmur.

The second pulmonary sound is frequently much accentuated, and this is very important as distinguishing patency of the duct from pulmonary stenosis with somewhat similar localization of murmur or thrill. On the other hand, in some cases it may be weak or even inaudible (Zinn, Gerhardt).

Schrötter described a paralysis of the left recurrent laryngeal due, he thought, to pressure upon the nerve by the enlarged patent duct.

The physical signs are very often obscured by those of other lesions, as malignant endocarditis or arteritis, chronic valvular disease, or other cardiac anomalies so commonly associated. The peculiar character of the murmur, its more or less prolonged rhythm, its localization, and that of the thrill when present, high up toward the left infraclavicular region, with the results of *x*-ray examination, remain, even in these complicated cases, of the first diagnostic value.

So-called aneurisms of the ductus Botalli give rise to no physical signs, being of small size and usually occluded by thrombus. They are generally said to be of little clinical significance, but death from rupture of their walls has been recently reported (Roeder,[1] Esser,[2] and Thore), and embolism from the thrombus within may lead to a fatal result.

So-called Aneurisms of the Ductus Botalli.—This term is used in the literature with a rather irregular application to denote a dilatation in whole or in part of a persistently patent duct. That the cases are not aneurisms in the strict sense is inferred by most writers. Rokitansky uses the qualifying word "so-called." Gruner says that arterial dilatation would often be a better word, as there is usually no change in the vessel wall, and he draws attention to the fact that in the usual bean-shaped form the constriction at either end makes the ductus appear larger to the eye than it really is. Klotz has suggested that, as in his injection experiments the duct is seen to be much larger at birth when distended with fluid than when contracted at postmortem, many of these small, so-called aneurisms, measuring less than 1 cm. in their greatest diameter, are really not even a dilatation, but are a simple distention of a patent duct to its full capacity by the coagulum within. Again, a further confusion exists in that the term is applied more widely by some writers than by others. Nevertheless, the cases recorded form a fairly well-defined group, which, from their rarity and from the fact that the duct is usually occluded by thrombus, are chiefly of pathological interest, although their occasional rupture, and also the risk of embolism from the thrombus within, increase their clinical significance. The first cases reported were by Billard, Thore, and other French writers; Rokitansky followed with his important monograph in 1852, and Virchow in 1856; full studies of the literature with original cases are to be found in the theses of Westhoff,[3] Voss, and Gruner.[4]

In what may be taken as the classical form (which is that described by Rokitansky) the ductus forms a spherical or ovoid tumor larger at the middle than at either end, but smallest toward the pulmonary artery, with which, as well as with the aorta, it communicates, filled with old or recent thrombus, and varying in size from a "cherry stone" (Billard) to a "hazel

[1] *Archiv f. Kinderheilkunde*, Bd. xxx.
[2] *Ibid.*, Bd. xxxiii.
[3] *Göttingen Diss.*, 1873 (quoted by Gruner and Voss).
[4] *Freiburg Diss.*, 1904.

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nut" (Thore), or even a walnut (Hebb, Binzer). Virchow's case may be taken as illustrative of the majority. In an infant "the arterial canal was dilated in its middle to the size of a small cherry, its opening in the pulmonary artery was the size of a pinhead, in the aorta that of a pea; the aneurism was filled by a thrombus, the pointed end of which projected into the aorta." In Hebb's case,[1] in a man aged forty years, an aneurism the size of a small walnut, filled with old clot, lay in the position of the duct, communicating with the aorta by an orifice one-eighth of an inch in diameter, and abutting against the obliterated left pulmonary artery and left bronchus.

All the cases recorded are in infants excepting that by Hebb. Rokitansky explains the condition as a dilatation of the middle part of the duct after involution has begun, due to an inequality of the obliterating process, which progresses with undue rapidity at the pulmonary end, so that the blood entering from the aorta cannot pass through, and, stagnating in the duct, forces its walls apart. The simple distention of a patent duct by a thrombus formed within it, and the annular contraction of either end, may explain these cases, except the few which, like Binzer's and Hebb's, are of very large size (Klotz).

Westhoff distinguishes three forms of aneurismal dilatation of a patent duct: (1) A cylindrical form, in which there is a uniform dilatation of the canal along its whole length, as in Luy's case, and Sander's, where it equalled in size the descending aorta, and Gerhardt's, measuring 2 cm. in diameter. (2) A funnel-shaped canal dilated at its aortic end and having a very narrow pulmonary orifice, surrounded (as in Willigk's case and in several by Rokitansky) with irregular tissue, where an occluding membrane had apparently been torn away. (3) The spindle-shaped or spherical aneurism, described in detail above as the typical form, and which is the only one recognized by Rokitansky as such, Westhoff's forms 1 and 2 being described by him as simple patency.

Of great interest have been the communications by Thoma[2] and Wagener. In Thoma's patient, aged twenty-six years, the aorta, from the isthmus downward for about 4 cm., was dilated in the form of a spindle, was lined by atheromatous plaques, and on its right wall opposite the left subclavian artery was a saccular aneurism, in the floor of which lay a small hole representing the lumen of the greatly shortened ductus leading into the pulmonary artery, which was here firmly adherent to the aorta. Microscopic examination showed this aneurism not derived from an expansion of the aortic end of the ductus, but to be a bulging of the aortic wall, which the writer thought was pulled to the right by the action of the contracted ductus. Rokitansky's 5 cases of funnel-shaped patency were explained by Thoma in the same way, and a special form of "traction aneurism of the infantile aorta" was thus established by him. In Wagener's 3 cases, aged respectively thirty-eight, forty-two, and twenty-three years, the duct formed a distinct canal with a small lumen open on the side of the aorta, where the orifice lay in the floor of a hollow in the wall of this vessel, and was sheltered by a distinct fold of aortic intima projecting downward from above, while the pulmonary end was closed in by a thin membrane, which bulged into the pulmonary artery. Although these cases correspond

[1] *Transactions Pathological Society*, London, 1893, xliv, p. 45.
[2] *Virchow's Archiv*, 1890, Bd. 122, p. 535.

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closely with those of Rokitansky and Willigk, which are classed by Westhoff as funnel-shaped aneurisms of the duct, and by Thoma as traction aneurisms of the aorta, Wagener, taking the older view of Rokitansky, places them with Gerhardt's forms 2 and 3 of simple patency, considering, on the basis of microscopic examination, the membrane closing in the pulmonary end to be of recent formation, and thinks that these cases argue against Thoma's contention that a patent duct at the bottom of such a sacculation of the aortic wall is always much shortened upon itself, and that they also settle the question of the possibility of the reopening of a previously closed duct, which Vierordt said was not yet proven.

Mycotic aneurism of the patent duct of the dissecting form has been described by Buhl.

Absence of the Ductus.—Absence of the ductus may occur, and is usually associated with hypoplasia and shortening, sometimes with atresia, of the pulmonary artery. It is explained as due to a primary failure of development of the fourth left branchial arch (which persists as the ductus), the stenosis of the pulmonary being secondary. In these cases a defect of the septum at the base is present, through which the aërated blood passes from the right heart to the aorta. Cases by Peacock[1] and King[2] are illustrations.

Anomalous Course.—Multiple origin is reported by Peacock[3] in a case of pulmonary stenosis, two small trunks arising at the site of the normal ductus and passing, the smaller into the left, the larger (which was cut short) apparently into the right pulmonary artery. In several cases the canal has opened into the left subclavian. In one case, of right aortic arch, the duct entered the descending aorta below the right subclavian and itself gave off the left subclavian artery.

COARCTATION OF THE AORTA.

This term applies to a well-recognized group of cases in which there is a narrowing or stenosis, amounting sometimes to a complete obliteration, of the descending arch at, or immediately below, the so-called isthmus of the aorta, which is that part of this vessel lying between the left subclavian artery and the insertion of the ductus arteriosus. During the period of fœtal circulation this segment is comparatively little used, and at birth is usually observed to be of slightly smaller lumen than the adjacent portions of the aorta, the difference in size soon disappearing under normal conditions. Thérémin states, as a result of his measurements of the normal infant heart, that in 80 per cent. a slight diminution in diameter exists in the isthmus during the first three months of postnatal life, after which a calibre uniform with the remainder of the arch is attained; and that in some 6 per cent. a slight difference remains throughout life which he does not consider abnormal unless it amounts to more than 2 mm. Bonnet classed as anomalous those cases in which the difference was about 3 mm.

Two distinct groups of cases are understood under the term. (*a*) A diffuse narrowing of the aorta at the isthmus (Bonnet's infantile type). In some of these cases in which the stenosis is marked, the circulation in the lower

[1] *Transactions Pathological Society*, London, vii, p. 83, and xi, p. 40.
[2] *Ibid.*, xxiii, p. 83.
[3] *Ibid.*, xxii, p. 88.

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part of the body is maintained by a large patent ductus arteriosus through which *the descending aorta appears to be a direct continuation of the pulmonary artery.* Such cases, being essentially the same in origin as coarctation, may be included with it. (*b*) A more or less abrupt constriction of the aorta at or near the insertion of the ductus arteriosus (Bonnet's adult type). Here, where coarctation is marked and has lasted some time, the establishment of an extensive collateral circulation frequently completes the pathological picture and lends distinctive clinical features to what is otherwise an obscure lesion.

Relative Frequency.—The figures in the literature are somewhat misleading in regard to this anomaly. Curiously little account is taken of its occurrence by many workers, and therefore the lesser degrees of coarctation are probably often overlooked in the postmortem room, and cases with well-marked vascular changes may escape diagnosis at the bedside. Thus, Dr. Libman has told the writer that a moderate stenosis at the isthmus is frequently observed in the autopsy material of the Mount Sinai Hospital, New York, where a special point of searching for the condition is made.

On the other hand, this subject has been so carefully worked over and brought up to date by successive writers, that its statistics are clearer and more accessible than is the case perhaps in any other chapter of congenital cardiac disease. Very probably, therefore, the 198 cases enumerated here are not far from being the full number of those recorded, whereas the total number of pulmonary stenosis or of septal defect (which anomalies have not been subjected, at least of recent years, to such careful repeated statistical analysis) must be much higher than that given by any author. For this reason Vierordt's statement that coarctation ranks next in frequency to pulmonary stenosis is probably placing the incidence too high. A truer estimate may perhaps be gathered from the fact that among 205 cardiac anomalies recorded in the *Transactions*, there are 22 of stenosis or obliteration of the aorta at the isthmus and 2 of entire absence of the aortic trunk between the left subclavian and the ductus, against 91 of pulmonary stenosis and 165 defects of the interventricular septum. Fawcett found only 18 cases of coarctation among 22,316 autopsies at Guy's Hospital.

The first case was reported by Paris in 1789. Craigie collected 10 from the literature in 1841, von Leeuwen 18 in 1850, Rokitansky 26 in 1852, and Peacock 40 cases in 1860. Barié, in 1885, gave a detailed review of 89 cases, in which he published the series of the above authors, with others from the literature. The fact that 6 of these are without autopsy findings reduces the number of Barié's cases for statistical purposes to 83. Schichhold, in 1897, added 30 to these, and Vierordt, in 1898, brought the number of recorded cases to 126. In 1903, Bonnet[1] published an article analyzing Barié's findings, and adding to these a synopsis of 77 additional cases which include the series of Schichhold and Vierordt, and make, together with the 83 cases collected by Barié, a total of 160, of which 55 are in infants and 105 in adults. In addition to these the writer[2] has collected records of 38 cases

[1] *Révue de Médecine*, 1903.

[2] Of these 38, 15 are from a series of 18 cases collected by Fawcett from *Guy's Hospital Reports* and published in 1902; 12 are from the *Transactions* reported by Chevers (vol. i, p. 55), Rees (vol. ii, p. 203), Peacock (vol. vii, p. 83), Lees (vol. xxxi, p. 58), Wilks (vol. xi, p. 57), Smith (vol. i, p. 52), Barlow (vol. xxvii, p. 41),

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not included by the above authors, 14 of which are in infants and 24 in adults, making a total of 198 cases, of which 69 are in the newly born, and 129 in patients over one year.

Pathogenesis.—The proximity of the stenosis to the insertion of the duct in the aorta suggests that the part which this vessel takes in the circulation, or the changes which go on in its form and tissues during its closure after birth, have an essential bearing on the production of coarctation. Many widely varying theories, all on this basis, have been proposed, but the problem cannot yet be said to be solved. Rokitansky (1852) assumed *in all cases*, as the essential condition, a persistence of the isthmus and a consequent weakening of its walls so that they yielded, in a way the healthy aorta would not do, to the traction exerted upon them by the contraction of the duct in its obliteration. Peacock, Eppinger, Kriegk, and Barié accept this theory of Rokitansky, but it must be noted that it cannot apply to those cases where the ductus remains patent.

Skoda (1855), writing directly after Rokitansky, opposed his theory entirely, and made the interesting suggestion that in those cases in which the isthmus was not obliterated at birth as a true anomaly brought about by an atrophy of the corresponding embryonic aortic arch, the tissue of the duct had extended into the wall of the aorta, which thus contracted as part of the same process by which the canal itself obliterates. This theory is adopted by Brunner (1888), with the modification that he supposes the transplantation of free portions of the ductus tissue into the adjacent wall of the aorta to occur, rather than its direct extension.

Bonnet gives the most satisfactory contribution to the subject. He divides the cases of coarctation into two types, according as these occur in the newly born or in adults, for each of which he claims an entirely different etiology, as follows:

1. The form described by him as that usually seen in the newly born is a diffuse narrowing of the isthmus, and is assumed to be of developmental origin; it is frequently associated with grave anomalies; in it the ductus arteriosus is often patent. The cases in this type fall again into two classes as regards their etiology: (*a*) When, as in the majority of cases, the stenosis is moderate in degree, it is explained on the theory of Rokitansky, as a persistence of the isthmus at birth, an arrested fœtal condition in which this segment fails to attain its normal calibre, and the cause of which is to be sought at or shortly before birth in a simple weakening of the vessel wall, the result probably of a lowered state of general nutrition. Thus Thérémin observed that in the case of his so-called normal infant hearts in which the isthmus was abnormally narrowed at birth, there was a history of premature delivery or of general weakness, and, conversely, that in 50 per cent. of infants born before term or weakly, marked narrowing was present. (*b*) Those rare cases of the infantile type, on the other hand, with an extreme degree of diffuse

of coarctation in infants, and by Peacock (vol. xii, p. 38), Finlay (vol. xxx, p. 262), King (vol. xxiii, p. 83), Habershon (vol. xxxix, p. 71), Mackenzie (vol. xxx, p. 66), in adults.

The remainder are reported by Preisz (*Jahrb. f. Kinderheilkunde*, xxxiii, p. 140), Lawrence and Nabarro, Hektoen, Dick (*Proc. Clin. Path. Society*, May 9, 1904), Osler (*Montreal General Hospital Reports*, P. M. No. 252), in infants, and by Pappenheimer (*Proceedings New York Pathological Society*, May, 1905, January, 1906, p. 177, October, 1906), Variot, Carmichael, one in *St. Bartholomew's Hospital Reports*, vol. i, series I, and the one in the Museum of Toronto University, in adults.

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stenosis, or in which the isthmus is reduced to an atrophic cord, are probably to be explained, as are also the few recorded cases in which there is a complete absence of the aorta between the left subclavian and the entrance of the ductus, as a failure of development in early embryonic life of that part of the fourth left branchial arch which corresponds to the isthmus of the aorta (Loriga). In this connection Bonnet suggests the possibility that the additional arch, described by recent embryologists as intervening between the fourth and sixth embryonic arches, may, in the early atrophy which it is said to undergo, involve the aorta at its insertion, and so lead to the stenosis.

2. Bonnet places in a second class as the adult type those cases seen usually after infancy is passed, in which the coarctation consists of a more or less abrupt constriction of the aorta at or near, often a little below, the insertion of the ductus. This condition, which is never seen in the fœtus, nor at birth before the closure of the ductus has begun, is, he thinks, not of developmental origin, but is to be explained on Skoda's theory of an extension of the peculiar tissue of the duct into the adjacent wall of the aorta, which thus contracts after birth along with the contraction of the arterial canal. As the malposed tissue is scanty and tends to be of a width corresponding to that of the narrow ductus, its contraction will have the effect of a narrow ligature or cord. These cases differ from those of the infantile type not only in the character of the stenosis, but also in that an extensive collateral circulation, giving rise to marked physical signs, usually develops and that serious anomalies are generally absent, this last fact arguing in favor of its postnatal origin. The ductus arteriosus may remain patent, but is usually obliterated.

Associated Anomalies.—The frequent combination of coarctation with other defects has been commented upon by many observers, but the distinction drawn by Bonnet between two types of cases, in one of which, that occurring in the newly born, grave anomalies are frequent, while in the adult form they are rare, although minor deviations from the normal are relatively common, offers a new and significant suggestion. A statistical analysis, on the basis of this division, of the 198 cases available from the literature gives interesting confirmation of his statements, and points to a radical difference in the etiology of the two groups. The following figures include as *minor* anomalies occurring chiefly in the adult type, anomalous semilunar cusps, irregular origin of the vessels from the arch, patency of the foramen ovale or duct, persistent left superior cava; and as *grave* anomalies, septal defects, transposition of the great trunks, congenital stenosis, etc.

Associated Anomalies in Coarctation in the Newly Born (69 Cases).

Series.	Absent.	Minor.	Grave.
Barié	0	3	3
Bonnet	13	11	25
New cases	0	2	12
Total	13	16	40

In Cases Over One Year ("Adult Type") (129 Cases).

Series.	Absent.	Minor.	Grave.
Barié	57	19	1
Bonnet	15	11	2
New cases	8	9	7
Total	80	39	10

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Thus among the 69 cases of stenosis in the newly born (dying under one year), in only 13 instances was there no other defect associated; minor defects were present in 17, and in 39 cases grave anomalies co-existed. Eight of these 69 cases were, as Bonnet points out, atypical of his infantile form; but the remaining 61 were of the milder grade of infantile stenosis, which is ascribed by him to a persistence of the isthmus due to the weakness of its walls. That is to say, there is frequently associated with the graver cardiac anomalies that form of coarctation which may reasonably be ascribed to a simple arrest of development in later fœtal life, and which is due probably to the depressing influences that led to the associated defects, or possibly in some instances to the disturbed circulation that results from the combined anomaly.

On the other hand, among the 129 cases in patients over one year (adult type), other anomalies were absent in 80 instances, minor defects were present in 37, and grave anomalies were associated in only 10 cases; moreover, 7 of these 10 had not the characteristic sharp constriction seen in the great majority of these cases, but were apparently a persistence of the infantile type; for in 3 (Chiari, Houel, MacKenzie) the pulmonary formed the descending aorta through a large patent duct, and the 4 others were in children of two to five years in whom the isthmus was simply diffusely narrowed. Transposition occurred in only one case (Fawcett), a child aged two years and nine months, with a stenosis apparently of the infantile type. Persistent left superior cava was noted only once (Bonnet).

Equally significant with this rarity of grave anomalies in the adult type of coarctation, suggestive, too, of some etiological factor as yet unknown, is the frequent association of a certain set of minor defects in the structures connected with the aortic arch, namely, irregularities in the origin of the great vessels, absence of the ductus (3 cases), double ductus (Hammernjk), and especially *anomalies of the aortic cusps*, which last are relatively so common as to seem to place their combination beyond the range of coincidence. Thus the *aortic valve was bicuspid* (in itself a rare anomaly) *in* 11 *instances;* its segments were apparently congenitally fused in 4; were increased to four with fusion of two of these in one (Fawcett); in one instance (Babington) a small supernumerary cusp had formed on the aortic wall above the others; and in one (Flaherty) there was subaortic stenosis, in the form of a membranous band below the cusps.

In the infantile type, on the other hand, amid so many grave anomalies, bicuspid aortic valves occurred only twice.

Pathology.—1. The diffuse stenosis of the isthmus usually observed in infancy is seen occasionally, but rarely, in later life. It is usually limited below by the ductus, and may begin above as a gradual diminution of the arch, or abruptly at the origin of the left subclavian artery, or, in a few instances, in which the isthmus itself appears to be placed higher up than usual, at the innominate or left carotid artery. The ascending aorta may be dilated or of normal calibre, and below the stenosis the vessel may remain smaller than usual, may return to its full size, or in cases where its descending portion is supplied by a patent duct, be much dilated. The lining of the stenosed area is usually smooth and healthy. In degree it may vary from a mere shade below the normal to a lumen of 1 to 2 mm. in diameter, or be represented in rare instances by a fibrous obliterated cord.

Among the total 198 cases, the pulmonary artery formed the descending

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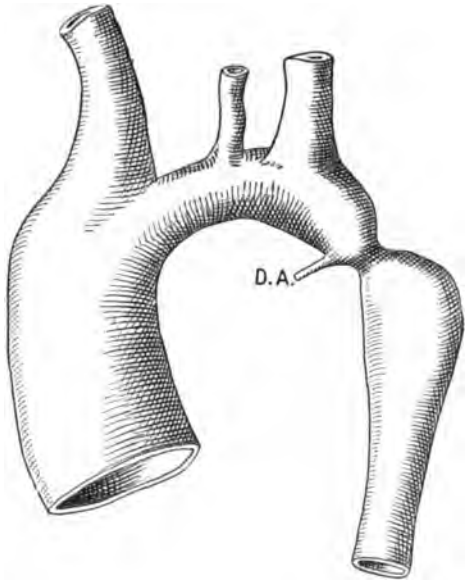
aorta through a large patent duct in 15 instances, in all of which marked coarctation of the infantile type existed. Twelve of these, those of Farre (2 cases), Oehl, Taruffi, Epstein, Katz, Crespin, Lees, Smith, Barlow, Dick, Osler, were in infants, and 3 in older subjects. In 2 other cases (Hicks and Barlow) the isthmus was entirely absent, the aorta ending in the left subclavian and the pulmonary continuing as the descending aorta. The ductus arteriosus was patent in 34 other cases of the 69 "newly born."

2. *Adult Type.*—A very different anatomical character and a much wider variation is presented. In typical cases the aorta is abruptly constricted at the level of, or a little above, or, most frequently, directly below the insertion of the ductus, as though by a tight ligature or cord, the groove thus formed being usually deepest on the convex side of the arch, which appears deeply

FIG. 43



Coarctation of the aorta in a woman aged twenty-seven years. Stenosis beginning just beyond the origin of the innominate artery; sharp constriction immediately below the insertion of the obliterated ductus (*D. A.*). (Reproduced from Bonnet's article, Revue de Médecine, 1903.)

indented as though cut through in a V-shaped manner (Fig. 43). The aorta on either side usually diminishes rapidly toward the stenosis in an hour-glass or funnel-shaped manner, described by Dickinson and Fenton in their case as "like two cones placed one against the other;" or it may be dilated on either side, giving a sausage-like effect (Bradley). Viewed from within, the inner surface of the constriction usually presents a projecting ridge or fold corresponding to the zone of constriction without. This may be so marked as to form a distinct septum bridging across the lumen, sometimes obliterating it entirely, as in Hammernjk's cases, or leaving a small central circular or triangular lumen, the constriction involving all the coats of the vessel (Laennec's case) or only its inner ones, the adventitia passing outside of it like a bridge. The constricted part of the wall may be formed of

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healthy tissue (Decker), or may present cicatricial fibrous thickening (Beraud).

In other cases the stenosis may occupy a wide area and appear from without like an annular band. Kriejk describes it in his case as a sort of resistant ring, enclosing the aorta like a cuff parallel to the axis of the vessel, and Mannaberg as a solid segment 0.5 cm. long just below the insertion of the duct. The lumen varies through all grades of stenosis down to one just admitting a bristle. In 20 cases of the 129 it was entirely obliterated, in some instances by a septum or diaphragm formed within (Laennec, Hammernjk, Brunner), but more frequently by the elongated annular form of constriction.

The aorta may be of normal caliber above and below the stenosis, or it may be slightly narrowed at its origin and dilated for a short distance up. The diminution in caliber not infrequently begins at the innominate or left subclavian artery, and in a certain percentage of cases is followed by a dilatation, below which again the characteristic tight constriction near the duct takes place; the effect being that of a *double stenosis*, as in the cases by Legrand, Maigne, Härlin, Alexais et Gilly, Waldstein, Pappenheimer, and others.

The aorta immediately below the stenosis is often widely dilated at the seat of origin of the intercostals. Hypoplasia of the vessel in its whole length existed in the cases of Hale White and Riegel; in the latter the stenosis at the isthmus was so slight that Vierordt questions the propriety of classing it with coarctation at all. In other cases the aortic walls, otherwise healthy, are noted as abnormally thin. The aorta may be smooth and healthy in its whole course, as in the cases reported by Brunner (complete obliteration), Cruveilhier, Almagro, Purser, and in the original one by Paris, or there may be extensive atheroma with calcification at the seat of stenosis, above or below it, or throughout the whole aorta. This was present in 34 of the 129 cases, in 8 of which it was definitely stated to be at the seat of stenosis, in 5 localized above, in 4 below, and in 6 diffuse throughout the aorta.

Rupture of the aorta occurred in 12 cases, in 7 cases at the ascending portion, and in 5 at the seat of stenosis. Aneurism of the arch occurred in 9 instances, and in 5 of these it was of the dissecting form.

In most well-marked cases of coarctation of the adult type the blood supply of the lower part of the body is maintained by the development of an extensive *collateral circulation*. The great vessels of the arch are often enlarged to twice their caliber, and the smaller branches involved are converted into thick, tortuous, dilated trunks. The principal anastomoses are carried on by the superior intercostals, the internal mammaries, and the posterior scapular branches of the transversalis colli *above*, with the first four aortic intercostals, the phrenic and superficial and deep epigastrics *below* the stenosis. Much importance has been ascribed by some writers to the part taken in the anastomoses by these latter vessels, which in some cases are greatly dilated, as in Reynaud's in which they were larger than the external iliacs. In other instances they are quite small, and Bonnet thinks that the path between the internal mammaries and deep epigastrics is of only secondary importance, the course of the bulk of the blood being *from* the branches of the ascending aorta into the upper aortic intercostals and thence into the descending thoracic aorta, from which the supply passes directly to the lower limbs. His view is supported by the extremely

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large size that the two first intercostals given off below the stenosis usually assume, and by the fact that in this region the aorta is sometimes much dilated.

Some evidence of collateral circulation was present in 56 of the 129 cases of the adult type. The particular branches involved and the degree of dilatation vary greatly even in cases of extreme constriction. In 3 instances out of the 129 (Barié, Pic and Bonnamour, and Dubreuil) it was expressly stated to be absent; in most of the remainder the collateral circulation was not mentioned, but this does not imply that it was always absent entirely, as minor alterations in the peripheral vessels are easily overlooked.

The ductus arteriosus was patent in 13 of the 129 adult cases. In some instances the ligamentum arteriosum is described as "solidified" or much thickened as though by inflammatory action. Among the 69 cases in infants under one year the ductus was patent 46 times.

Marked hypertrophy with dilatation of the heart is rare in infants, but occurs in the majority of the older cases, being noted in 77 out of the 129. It is stated by most authors to be the direct result of the obstruction in the course of the descending arch, but the relation of the two conditions is rendered uncertain by the frequent association of chronic valvular disease, which must itself be a factor in the hypertrophy. Moreover, a few cases are recorded (*e. g.*, Reynaud's, aged ninety-two,) in which, with marked constriction or, even, as in Brunner's case, an obliteration at the insertion of the duct, the heart has remained normal throughout life. This was stated to be the case in 9 of the 129 cases. Although this is a small percentage, it proves that the new channels provided for the blood by the dilated collaterals may be sufficient to carry on the circulation without increasing the work of the heart. In Dumontpallier's patient, aged thirty-nine years, in whom the stenosis was produced by a septum with triangular central opening, 13 mm. in diameter, and the heart was not hypertrophied, the collateral circulation was carried on chiefly by the aortic intercostals and the vessels from the subclavian, the anastomosis between the internal mammary and the epigastrics being little developed.

On the other hand, an analysis of the 77 cases with hypertrophy shows that while 44 were complicated with chronic valvular lesions or other cardiac defects, in the remaining 33 no cause was present except the coarctation itself. Of these 33, hypertrophy was confined to the left ventricle in 7, and involved the whole heart in 26, of which latter the left ventricle especially was enlarged in 8. An interesting point is that in 19 of the 33 the collateral circulation was either stated to be absent or was not mentioned, and in 4 more it was not much developed, the only sign noted being a dilatation of the great vessels of the arch. In the 12 remaining cases a collateral circulation had developed, but in 4 of these the cardiac hypertrophy was only slight. These facts argue that even in extreme degrees of constriction the heart may remain normal in the presence of an adequate collateral circulation, but that when this becomes insufficient, cardiac hypertrophy and dilatation supervene.

Age and Sex.—A remarkable predominance of the anomaly in the male sex is noted by all writers. This point is frequently not stated in regard to the newly born. Among 121 of the 129 cases over one year, 81 were in males, and 40 in females.

That the stenosis does not necessarily interfere with the duration of life

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is proven by the fact that 7 patients died in the sixth and 6 in the seventh decade, while one (Reynaud's) lived to the age of 92. More than half of the remainder, however (56 cases), died between the ages of twenty and forty years; indicating that, in the anomalous conditions of the circulation that prevail, the system is not, as a rule, equal to the full demands of the stress of normal existence.

In the 129 cases over one year death occurred as follows:

	Cases.
1 to 5 years	7
5 to 10 "	4
10 to 15 "	4
15 to 20 "	16
20 to 30 "	31
30 to 40 "	24
40 to 50 "	15
50 to 60 "	7
60 to 70 "	9
Over 70 "	1
Adults (exact age not mentioned)	11

Symptoms and Course.—Coarctation in infants is of little clinical significance, except in so far as it may complicate other grave anomalies. In the adult type it is a condition of the greatest interest and importance. The following statements are based on the reports of the 129 cases in subjects over one year:

Symptoms when present may be distinguished as those associated with the lesion and those of the cardiac insufficiency which frequently supervenes. As characteristic of the overtaxing of the altered circulation, in which the blood supply to the head and upper extremities is freer than that to the lower part of the body, may be mentioned: violent pulsations (Flaherty's case), plethora with sleeplessness and continuous buzzing in the ears (Legrand), violent headaches (Hammernjk), lividity of the face (Chevers, Purser, Kjellberg), suffusion of the head and neck (Moore), epistaxis and hæmoptysis (Flint); in Dubreuil's case, a vascular surcharge of the head and chest contrasted with an atony of the subdiaphragmatic viscera; in that of Redenbacher, a boy aged seven years, with a stenosis at the isthmus admitting a crow-quill, and extensive collateral circulation, the development of the head and upper extremities was in advance of that of the lower part of the body. Severe thoracic, epigastric, or abdominal pain and vomiting of long standing (Roemer's case), or pains in the back or lower extremities (Lebert) occur, and may perhaps be due to the local effect of the constriction. Of significance is Muriel's report of a man aged twenty-five years, who was always weakly, and who developed severe pains in the back and symptoms of aneurism of one of the large vessels of the chest; postmortem a dense mass of enlarged glands the size of a hen's egg was found adherent to the aorta at the point of its constriction; it had eroded the dorsal vertebræ. Precordial pain and oppression, dyspnœa, and severe palpitation indicate the cardiac strain. Cyanosis is extremely rare except as a terminal event; in only 2 uncomplicated cases in the whole series (Almagro and Carmichael), in both of which the ductus was patent, was a true congenital cyanosis present throughout life. Lack of development was noted three times, delayed menses once. Many end with a stage of failing compensation, which, in those not complicated by chronic valvular disease, is usually identical

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with that of mitral incompetence, generalized œdema, ascites, cough with blood-stained sputum or repeated hæmoptysis, and orthopnœa.

Symptoms are (*a*) absent, (*b*) late in developing, or (*c*) present throughout life. (*a*) In some of the most well-marked cases of constriction or even obliteration at the isthmus, symptoms are absent throughout life. The condition may be quite latent, and constitute, in Barié's words, a "*surprise d'amphithéatre*" at the autopsy, death occurring from some intercurrent, independent disease. Thus Crisp describes a chance finding of a stenosis admitting a goose-quill in a soldier aged forty-eight years, who had been in excellent health and had died accidentally, and Scheiber, complete obliteration of the descending aorta in a man aged forty-one years, dying of pneumonia, who showed no signs of heart disease. In other instances physical signs may be present, and the lesion be unexpectedly revealed during life.

In these latent cases sudden death may occur. This is sometimes apparently directly due to the lesion, as in Kjellberg's case of a stenosis in a seemingly healthy woman aged twenty-eight years, who died when stooping to put on her boots. In most instances a rupture of the heart or aorta is found, (Lüttich, Barker, Wise, Legg, and others). Death took place without previous warning or symptoms in 16 of the 129 cases, constituting an event of sufficient frequency to have an important medico-legal bearing.

(*b*) A large proportion of the cases are in able-bodied, vigorous men, in whom the lesion long remains latent, symptoms developing as the altered circulation becomes overtaxed, or on the intercurrence of some complicating condition, especially endocarditis. Bonnet draws attention to the fact that the symptom of intermittent claudication is always absent, even in the most extreme degree of coarctation, indicating that the blood supply to the lower limbs is physiologically sufficient. He thinks that cardiac strain is a minor factor in the final breakdown of these cases, and that this is induced rather by the lowering of the general resistance. Certainly a history of rheumatism or endocarditis antedates the appearance of symptoms in a remarkably large percentage, while in others pneumonia, influenza, or septic processes have occurred. Not infrequently, symptoms developing late in life are entirely cardiac in character, cases otherwise latent terminating with a stage of failing compensation which may be due to the lesion itself, or to the chronic valvular disease so often associated.

(*c*) In a few instances only, symptoms of some obstruction in the cardio-vascular system are present throughout life. Quinquaud's patient, a youth aged nineteen years, suffered from infancy with intense palpitations and violent dyspnœa, so that he could not join in play, and œdema of the extremities developed shortly before death, which occurred suddenly. Erman's patient was weakly and had always suffered from dyspnœa. Death took place at 19, after seven and a half months of failing compensation. Lebert's patient, aged twenty-two years, had long had epistaxis and dyspnœa, and developed cardiac symptoms in the last two years.

Physical Signs.—Physical signs bear no constant relation to the symptoms, but may be present where these are quite lacking. Nor, on the other hand, do they correspond to the degree of the constriction, nor to the extent of the collateral circulation, both of which may be developed to an extreme degree without yielding any evidence of their presence. The most marked signs appear to be produced in association with chronic valvular

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disease or bicuspid aortic valves, or with the relative mitral incompetency of the later stages of the cardiac dilatation that frequently supervenes, in which cases the murmurs formed in the heart may be propagated along the vessels. The signs peculiar to the lesion, however, may best be studied in uncomplicated cases. They are both vascular and cardiac, and are present in varying degrees and combinations in the majority of cases.

Vascular.—These depend chiefly upon the inequality of the circulation in the upper and lower halves of the body, and upon the unusual appearances presented by the dilated collaterals. In well-marked cases the vessels of the upper half of the trunk may be seen pulsating, the subclavians, as a rule, more markedly than the carotids; and pulsations may be traced in many cases along the abnormally dilated and tortuous vessels occupying the course of the internal mammaries on either side of the sternum, or the posterior intercostal or scapular arteries behind. In Libman's patient there was a varicose mass beneath the skin of the abdomen; in Flint's, both supraspinous fossæ were occupied by a network of tortuous pulsating vessels; in Læudet's, small arterial dilatations extended over the middle of the thorax both in front and behind, and were most marked at the posterior border of the left axilla and in the left supraspinous fossa, where they formed tortuous, thickened vessels, pulsating synchronously with the radials. Along the whole course of these a murmur, usually postsystolic in rhythm, but sometimes systolic or double, may be heard, and very rarely, as in one case only of the 129, that of Flint, a slight thrill may be felt.

The radial pulse is frequently hard and full, and may be unequal on the two sides. The lower extremities may contrast strangely with the upper half of the body in the absence of all visible pulsations. On examination the pulse in the abdominal aorta and femorals is either very weak or absent, while the murmur usually audible on pressing over the femoral with the stethoscope cannot be heard. In Bonnet's case, diagnosed before death, no pulse could be felt in the abdominal aorta or femorals. There was epigastric and episternal pulsation, and pulsation of the temporals, and an artery pulsating visibly and as large as the radial, over which an intense systolic murmur could be heard, ran downward between the vertebral column and the inner border of the left scapula. On the right side of the column a similar but less strong pulsation could be felt, but no murmur was heard.

Hornung's patient, a man aged twenty-seven years, is an example of an extreme stenosis not producing any symptoms, but with marked physical signs, in whom death occurred suddenly from rupture of the aorta. There was energetic pulsation and a systolic murmur over the carotids and subclavians. At the inner border of the scapular region were sinuous pulsating vessels. The radial pulse was hard and resistant, and there was no pulsation in the abdominal aorta, popliteal, posterior tibial, or pedal arteries. As long ago as 1839, Mercier diagnosed a case in which there were visible pulsations in the intercostals, a marked bruit at the lower angle of the left scapula, and a very weak pulse in the lower extremities, with epistaxis and symptoms of failing compensation for three months before death.

Cardiac.—The heart's action may be tumultuous, with a heaving impulse, and the organ may present evidences of enlargement, particularly of the left ventricle. A precordial thrill is rare, and was present in only 2 of the cases. The heart sounds are usually heard distinctly at all areas, and may be quite

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pure, or accompanied by loud murmurs, usually systolic or postsystolic in rhythm. In several of the cases they were accompanied by a systolic murmur at the apex, audible also in the back. In Hornung's patient a rough murmur was heard at the aortic area, most marked between the left clavicle and the third rib. In Decker's, diagnosed before death, a woman aged nineteen years, with complete obliteration at the isthmus and no complicating valvular disease, a rasping murmur filling the whole systole was heard at the apex, and could also be traced along the thickened, tortuous, and dilated arteries, among which the superior epigastric, the long thoracic, and the dorsalis scapulæ formed pulsating cords; the heart was hypertrophied.

Diagnosis.—When such symptoms and signs as the above occur together a very distinctive clinical picture may be formed. It must be remembered, however, that they may be entirely absent, or present only in a fragmentary way, such as may awaken suspicion of the reality, yet render a positive diagnosis impossible. The fact that physical signs as well as symptoms usually do not remain stationary, but progress to a more definite development, furnishes the clue by which the presence of the anomaly may perhaps best be traced. A pulsation at an abnormal area, or a superficial murmur of unusual site, noted and watched, may lead to a second later examination, at which the full development of the condition may be revealed.

Even where symptoms are present, the diagnosis may be very difficult between a constriction of the descending aorta at the isthmus and obstruction of this vessel or its branches by aneurism, or by the pressure of a mediastinal tumor. The absence of any considerable area of dulness, the transmission of the murmur for long distances along the branches of the ascending arch, the remarkable extent to which the collateral circulation is sometimes developed, above all, the results of x-ray examination, contribute differential points in favor of coarctation. In perhaps no other pathological condition are more extensive changes compatible with fewer evidences during life.

The later stage of cases, in which vascular phenomena are lacking and failing compensation develops, may be impossible to distinguish from that of organic insufficiency of the mitral valve.

Termination.—The cases may be divided into three groups: (1) The condition may be latent throughout life and not interfere with its duration in any way. (2) Both in latent cases and in those presenting symptoms throughout life death may occur suddenly, by a systole, from rupture of the heart or aorta, or from causes unknown. (3) Death may follow a stage of broken compensation, which may be preceded by symptoms characteristic of the lesion, or may develop suddenly in an apparently healthy subject.

HYPOPLASIA OF THE AORTA AND ITS BRANCHES.

Hypoplasia of the aortic system may be described as that condition in which the lumen of the arterial vessels in the greater circulation remains abnormally small and the walls unnaturally thin and elastic. The heart may also be reduced in size or may undergo a compensatory dilatation and hypertrophy which involves especially the left ventricle, but may extend

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to the whole organ, and is usually succeeded by a marked degree of secondary dilatation. The intima of the narrowed vessels is usually thin and delicate, but may be diseased. The subjects are, as a rule, pale individuals of delicate frame, who present signs of retarded development, such as a delayed advent of the signs of puberty. Anomalies of the sexual organs frequently occur. The general health is usually fair until early adolescence, when the condition generally manifests itself after some unusual physical strain has been endured, by the sudden appearance of failing compensation. The course is then progressively downward, ending in death. In women, who are by natural conditions less exposed to undue muscular exertion than are men, this stage of cardiac insufficiency may not supervene, but the disease may run its course under the guise of a chlorosis. By some observers (Ortner, Hiller) the narrowing of the vessels is thought to predispose to the infectious fevers, and a special group of cases in which death has occurred from typhoid fever is described. It is also seen in young anæmic subjects dying of pulmonary tuberculosis.

There has been some debate as to the pathological significance of the condition. Several authors (Sutor, Lewinski) have maintained that the greater elasticity of the walls of the vessels compensates for their smaller caliber, and so prevents undue strain upon the heart. A number of recent statistical contributions have, however, fairly demonstrated that hypoplasia of the aorta must be given a place in pathogenesis as one of the special causes of cardiac disease. The clearer definition of this condition may be ascribed chiefly to the articles of Ortner, Spitzer, Burke, Apelt, and Sigmund van Ritoók.

Typical cases were described by Morgagni in 1761 and by Meckel in 1788. Rokitansky defined the condition in 1838 and commented upon its association in some instances with defects of the external genitalia. Wilkinson King, in 1841, remarked upon its importance, and deplored the fact that it was not generally recognized by clinicians. Bamberger, in 1843, noted the association of chlorosis with a small aorta. But in general the subject attracted little attention until Virchow, in 1872, published a series of cases illustrating the frequency of a small elastic aorta and a small heart in chlorosis, and suggested an etiological relation between the two conditions. He explained the absence of compensatory hypertrophy of the heart in some cases and its presence in others, as depending upon the degree of diminution of the lumen of the vessels, the volume of the circulating blood, the elasticity of the vessel wall, and the amount of work done by the individual. Thus, it is readily understood that more strain may be thrown on the heart of a plethoric individual whose bloodvessels, although dilated, have atheromatous calcified walls, than on that of a chlorotic subject with the small but elastic vessels of a typical hypoplasia.

Much discussion ensued upon this presentation of the subject, and many contributions followed, so that the recorded cases, estimated by Vierordt as only 30 in 1898, now number about 100 (Apelt). A diagnosis confirmed by postmortem was first made by Fraentzel in 1888. Ortner, in 1891, dwelt chiefly on the medico-legal aspect of the subject, and emphasized as pathognomonic an absence of the jugular pulsation in the episternal notch in cases in which the upper border of the cardiac dulness is high. Burke remarks that this sign is not constant. Spitzer (1897) attempted by a study of the recorded material to place the condition on a more definite

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clinical basis. He pointed out that while the cases usually terminate with failing compensation, this resembles the end stages of chronic valvular disease only in a general way, a certain incongruity in the details existing; that the symptoms are in general those of a cardiac overstrain due to muscular fatigue, and have a progressive tendency to grow worse; that during the stage of broken compensation the cardiac dulness is usually much enlarged, and that the sounds are generally clear, with marked pulmonary accentuation, although occasionally accompanied by murmurs. Like Virchow, he noted as characteristic a remarkable *pallor*, but he ascribed it not to a diminution of the hæmoglobin, which he found usually 90 to 100 per cent., but to the reduction in size of the vessels through which a smaller quantity of blood coursed beneath the skin.

Burke[1] (1901) gives an historical review of the subject and a full account of all the cases on record. From a statistical study he seeks to establish certain clinical conclusions as to the development of the terminal cardiac symptoms, inquiring especially into the duration of this stage, and whether the degree of hypoplasia has any direct relation to its development. He divides the material before him into the four following groups:

1. Hypoplasia of the aorta in the so-called blood diseases, as chlorosis, pernicious anæmia, hæmophilia.
2. Hypoplasia in association with infectious diseases, considered as predisposing to these or tending to their fatal termination.
3. Hypoplasia with general dystrophies, as acromegaly.
4. Hypoplasia presenting the picture of a cardiac lesion, the mass of the cases belonging to this last group.

The obscure question of etiology is discussed at length in Burke's article. In a few cases, as in the cachexias of tuberculosis and other wasting diseases, an atrophy of the aorta is suggested. In the majority some congenital defect is supposed, or possibly, in some instances, a congenital tendency in the vessels to dwarf growth. The view of a congenital origin was brought forward by Rokitansky and was supported by him and by Virchow on the ground of the frequent association of other anomalies, especially in the generative and circulatory systems.

Apelt[2] adds to an admirable critical *resumé* of all the preceding work an account of two classical cases, both of which were diagnosed by Lenhartz during life. The subjects were aged seventeen and twenty-one years, and were without hereditary predisposition. Both were young men of slight build and medium size, who had been capable of the usual amount of physical exertion, and had presented no symptom of disease. Both passed through a period of unusual physical strain just before the sudden onset of symptoms, which took place a few weeks before death. The picture was that of an acute dilatation of the heart with slight terminal cyanosis, œdema, ascites, the cardiac area enormously increased, and the pulmonary second sound markedly accentuated. The heart sounds were pure except toward the close in one patient, in whom a systolic mitral murmur developed. Postmortem, in both cases, the arteries were throughout thin, delicate, elastic, and of diminished caliber, and there was moderate hypertrophy with great pathological dilatation of the heart, although its valves and chordæ tendineæ

[1] *Deut. Arch. f. klin. Med.*, 1901, No. 71, p. 187.
[2] *Deut. med. Woch.*, 1905, p. 1186.

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were thin, delicate, and healthy. Microscopic examination revealed an entire absence of fatty degeneration of the myocardium.

Apelt gives the following table of measurements of the heart and aorta in these 2 cases as compared with the standards of Vierordt and Schiele-Wiegandt for young men from fifteen to twenty-five years of age, and of Thoma from nineteen to twenty-one years.

	Normal.	Case I.	Case II.
Weight of heart	236 gms. (Thoma)	.....	495 gms.
Breadth of heart	9.5 cm.	15.0 cm.	13.0 cm.
Height of left ventricle	9.4 cm.	14.0 cm.	12.0 cm.
Diameter of ascending aorta	3.2 cm.	1.6 cm.	1.9 cm.
Circumference of ascending aorta	6.7 cm. (Krause)	5.0 cm.	5.5 cm.
Circumference of descending aorta	5.0 cm.	4.0 cm.	4.4 cm.
Diameter of the femoral	0.5 cm. (Thoma)	.....	0.4 cm.
Diameter of common carotid	0.6 cm. (Thoma)	.....	0.4 cm.
Thickness of aortic wall	1.0 cm. (Krause)	.....	0.75 cm.

Van Ritoók[1] analyzes 73 cases, of which 56 are from the literature and include the series of Burke and Apelt, and 17 are from personal observation. He attaches less importance to the congenital origin of the hypoplasia, and also points out that, although Burke and Apelt have considered it a condition which may in typical cases be readily diagnosed, Quincke and Rauchfuss placed it rather among those admitting only of surmise during life.

He enumerates the following points as of diagnostic value: (1) The youth of the patient. (2) Marked and obstinate anæmia persisting in spite of all treatment. (3) The early development of fatigue in a young individual on slight physical exertion. (4) Subnormal temperature or only slight rise of temperature in febrile diseases. (5) Palpitation. (6) Hypertrophy of the left heart. (7) Acute cardiac insufficiency developing after comparatively slight physical strain. (8) Diminished resistance to infectious diseases.

ANOMALIES OF THE AORTIC ARCH AND ITS BRANCHES.

Double Aortic Arch.—Various curious anomalies occur which may be traced to the arrest of development of the primitive arches, so that certain of these which usually atrophy remain persistent. The most interesting of these and one of some clinical importance is that known as double aortic arch, in which the peculiar effect is produced of a vascular circle surrounding the œsophagus and trachea. The aorta divides near the beginning of the transverse arch into two large trunks. Both of these pass to the left and join each other just after the insertion of the ductus, enclosing between them an elliptical space in which the two viscera lie. The posterior member of the pair is usually the larger, and, therefore, projects above the other, appearing as the true arch of the aorta. From it arise the right carotid and subclavian. The smaller anterior limb lies below and parallel to the upper, appearing like a loop from it. It gives off the left carotid and subclavian, either as a large trunk or as two separate vessels. Such a case was described by Curnow[2] in 1874. The specimen was obtained in the dis-

[1] *Zeitschrift für klin. Med.*, 1906.
[2] *Transactions Pathological Society*, London, 1874, vol. xxvi, p. 23.

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secting room from a woman aged eighty-seven years; the trachea lay quite free within the ring. In a similar case reported by Hamdi,[1] in a woman aged forty-five years, dying of an independent condition, the trachea was compressed so that its lumen was distinctly ovoid and the œsophagus was also slightly depressed. Although no symptoms had been produced, the deformity of the trachea was sufficient to prove the possibility of a serious or even fatal constriction.

Poirier, in 1896, knew of only 8 recorded cases of this anomaly. Henle explains the posterior limb of the double aorta as a persistence of the fourth right arch to form the aorta. The anterior limb represents the fourth left arch, and the two unite below the ductus arteriosus to form the descending aorta as in the embryo and as is persistent in the amphibia.

Right Aortic Arch.—This condition occurs, but is rare except in association with transposition of the other viscera. A *left* innominate and a *right* carotid and subclavian are given off, and the aorta arches over the right instead of the left bronchus, while the ductus enters the descending arch below the origin of the right subclavian. It is explained as the persistence of the fourth right branchial arch to form the aorta, as is normal in the bird. A curious case of a right aortic arch in which the left subclavian is given off from the large patent ductus is described and figured in *St. Bartholomew's Hospital Reports*, 1884, vol. xx, p. 273. The ductus arises from the left pulmonary artery and crosses to the right to enter the arch at the usual level below the origin of the right subclavian. Just before its termination it gives off a left subclavian of normal size. The unaërated blood from the right heart must have entered the arterial circulation.

Miscellaneous Anomalies.—The right subclavian may arise from the descending arch beyond the left, the commonest anomaly of the great trunks. Yeo describes a constriction of the aorta three-quarters of an inch above the valves, produced by a fibrous thickening of the wall and nearly closed by recent vegetations. The pulmonary artery was abnormally short, and its posterior branch crossed the aorta and was thought to have constricted it. The left ventricle was much hypertrophied. The patient, a boy aged ten years, had no symptoms until a malignant endocarditis developed, but a systolic murmur was heard all over the chest, most marked at the base of the heart, and the cardiac dulness was enlarged.

ANOMALIES OF THE CORONARY ARTERIES.

Anomalous Origin from the Pulmonary Artery.—In this a vessel arises from a sinus of Valsalva of the pulmonary artery, and, meeting the branches from the aortic coronaries, produces a remarkable anastomosis of a cirsoid character. Two such cases have been reported by Brooks[2] and one by Krause,[3] and a fourth, unique in several particulars, in the McGill Museum was destroyed by the recent fire.

In Brooks' first case, a vessel the size of a crow-quill sprang from the right anterior sinus of Valsalva of the pulmonary and passed down over the

[1] *Deut. med. Woch.*, 1906, p. 1410.
[2] *Journal of Anatomy and Physiology*, 1886, vol. xx, p. 26.
[3] *Zeitschr. f. Rat. Med.*, 1865, vol. xxiv (quoted by Brooks).

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infundibulum of the right ventricle, there anastomosing with the aortic coronaries. Its walls were thin and venous in character, but there was no marked dilatation of the inosculating branches. In his second case a large anomalous artery arose from the same situation. It gave no branches to the heart but passed to the left and upward to enter a complicated mass of thin-walled arteries, which lay around the main pulmonary trunk and passed up along the trachea and behind the aortic arch. This mass received three other large vessels. One descended to it from the left subclavian, one ascended from the right aortic coronary, and one entered it immediately from the posterior aspect of the transverse aortic arch. Krause's case is very similar to this.

The McGill specimen was from a woman aged sixty years, who died accidentally. The right coronary arose in its normal situation from the anterior sinus of Valsalva of the aorta by a much dilated orifice, and beside it a second small accessory trunk arose which was distributed only to the immediately adjacent myocardium. Directly after its origin the right coronary expanded into a huge thick-walled loop the size of a crab-apple, which projected upward some 2.5 cm. above the subepicardial fat. The descending branches of the right coronary were given off from the loop and the main trunk of the vessel emerged from it about 4 cm. away from the arota, and coursed along the auriculo-ventricular groove. All were wide, thick-walled, tortuous channels. No coronary arose behind the left posterior aortic cusp in the normal situation of the left coronary, but instead a large patulous opening lay in the floor of the dilated posterior sinus of Valsalva of the pulmonary artery. From this sprang a large thin-walled trunk of venous character, which divided about 1 cm. beyond its origin into two large branches, one of which ran to the left in the auriculo-ventricular groove in the course normally followed by the transverse circumflex branch of the left coronary artery, while the other ran downward along the front of the interventricular septum in the position of its descending branch, and was here expanded into a large triangularly shaped venous sinus, 2 cm. in its widest diameter, and diminishing in size toward the apex. In the floor of this sinus were several thick-walled septa behind which large vessels opened into it from the myocardium. There was slight hypertrophy and dilatation of the heart, and fibrosis of the endocardium of the left ventricle.

In his article Brooks discusses the interesting question of the circulation in the anastomosing vessels, in which blood from the systemic and pulmonary circulations must have mingled. He suggests that the direction of the current must have been *toward* the cirsoid aneurism in the coronaries arising from the aorta, and toward the right ventricle in the coronary that arose from the pulmonary artery, which would thus drain the mass and would also send some arterial blood to the lungs. The absence of a cirsoid condition in his first case he explains as due to a more indirect and less free anastomosis.

In the McGill specimen the peculiar septa in the floor of the large venous sinus formed by the descending branch of the anomalous vessel, strongly suggested that the course of the blood was *toward* the pulmonary artery. This case is additionally interesting from the fact that the anomalous vessel was here clearly the left coronary, which was absent from its normal situation and arose from the pulmonary. Both this and Brooks' second case were in elderly subjects, and the condition had not produced any manifestations during life.

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Miscellaneous Anomalies.—Accessory coronaries may be present or both vessels may arise behind a single aortic cusp, or there may be a complete absence of one. A case has been recorded of an anomalous coronary sent to the lungs in pulmonary atresia. The descent from the aortic arch of a single artery to supply the myocardium has been described.

ANOMALIES OF SYSTEMIC AND PULMONARY VEINS.

Systemic Veins.—Persistent left superior cava is probably the commonest of these anomalies. It is not infrequent in conjunction with other cardiac defects. Although of little clinical importance, it is of great interest in doubtful cases, as indicating the developmental origin of the associated condition.

Absence of the superior vena cava is reported by Habershon[1] in a man aged thirty-seven years. The usual opening of the superior vena cava in the right auricle was represented by thick, smooth, white endocardium, like a closed foramen ovale, and there was extensive development of a collateral circulation through the azygos major. One pulmonary cusp was absent. The author thought both conditions congenital.

Pulmonary Veins.—Of more clinical importance but probably of greater rarity are anomalous conditions of the *pulmonary veins*. One or more of these may be displaced to the right and empty either into the superior vena cava or the right auricle. Such cases are usually associated with a defect of the interauricular septum at its upper or posterior part. Reference has already been made to the series of cases published by Ingalls and others in this connection. Nabarro[2] describes the pulmonary veins opening into the coronary sinus in an infant aged five and one-half months, in whom all the blood from the systemic circulation must have passed through the patent foramen ovale. The pulmonary veins of both sides may enter the left auricle as a single or as two trunks, the original single vein not having been taken up in its wall as in the normal development.

DIAGNOSIS, PROGNOSIS, AND TREATMENT OF CONGENITAL CARDIAC DISEASES.

Differential Diagnosis.—In the diagnosis of congenital cardiac diseases two questions are to be considered: a congenital is to be distinguished from an acquired lesion, and the differentiation may be attempted of the particular defect. The first of these is the more important as well as the simpler problem. It is necessary both for a wise prognosis and for proper treatment to recognize the congenital nature of the lesion, and this can usually readily be done. The following conditions are significant of the presence of a defect: (*a*) The youth of the patient. (*b*) A history of symptoms originating in early childhood or in infancy, and of the absence of any event, as rheumatism or endocarditis, which could have led to an acquired lesion. (*c*) The character of the cyanosis when this is present,

[1] *Transactions Pathological Society*, London, 1876, vol. xxvii, p. 79.
[2] *Journal Anatomy and Physiology*, 1902-03, vol. xxxvii, p. 387.

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and of the symptoms associated with it. (*d*) The presence of atypical physical signs. In this connection the following general statements, abstracted from Hochsinger, are valuable: (1) In young children the combination of heart murmurs with a great increase of the cardiac dulness to the right and feeble apex beat is suggestive of congenital disease, in which the right heart is usually chiefly enlarged, while the left is only slightly altered. On the other hand, in acquired endocarditis in children, the left heart is chiefly affected and the apex beat is visible, the dilatation of the right heart developing late and not materially changing the strength of the apex beat. (2) In childhood a loud, harsh, musical murmur, with normal or only slight increase in the heart dulness, occurs only in congenital heart disease. (3) The absence of murmurs at the apex and their presence in the region of the auricles and over the pulmonary orifice is always an important element in diagnosis, and points rather to a septal defect or to pulmonary stenosis than to postnatal endocarditis.

The diagnosis of the various cardiac defects from each other is a difficult and often an uncertain task. Fortunately it is also of less importance to the practitioner, whose line of action is usually outlined by the general knowledge that the lesion is of congenital origin. As conditions which admit of diagnosis in typical cases, and which are of sufficient frequency to be considered among the probabilities, may be enumerated: defects of the cardiac septa, pulmonary stenosis or atresia, patency of the duct, and coarctation of the aorta. Transposition of the arterial trunks and hypoplasia of the aorta have been repeatedly recognized during life, but this has been done chiefly from the general clinical picture and from the *negative* character of the physical signs.

Cyanosis is the rule (to which a few exceptions occur) in pulmonary stenosis and atresia, in complete defects of the septa, as biloculate or triloculate heart or persistent truncus arteriosus, and in transposition of the arterial trunks. It is frequently absent, but may be present, and this especially as a terminal event, in patent foramen ovale and in defects of the interauricular and interventricular septa. Cyanosis is usually *absent* in patent ductus and in coarctation and hypoplasia of the aorta.

Physical signs are inconstant but the following general statements may be made: A systolic murmur localized over the upper part of the precordium and of diminished intensity or inaudible at the apex is characteristic of pulmonary stenosis and of septal defects. It may in a few cases be heard best at the apex, and it may vary in rhythm, particularly in septal defects. Both in pulmonary stenosis and in patency of the duct the murmur frequently has its point of intensity high up and may be heard beneath the left clavicle. Murmurs of congenital lesions, when heard in the back, are usually due to patency of the duct or to septal defects. Continuous murmurs beginning toward the close of systole, point to a patent ductus.

Coarctation of the aorta is to be recognized by the evidences of the collateral circulation and of the hypertrophy of the left heart. My colleague, W. S. Morrow, suggests that the sphygmomanometer may give a diagnostic hint by indicating the reduction of pressure in the vessels of the lower extremities.

The differential diagnosis is further discussed in the chapters upon the different defects. In the most complicated forms of congenital cardiac disease physical signs may be conspicuous by their absence.

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Prognosis.—The duration of life has been considered in detail in connection with those defects that are of clinical interest, but a few generalizations may be made. The prognosis varies with the lesion and includes a wide range of possibilities, but is in general bad; its gravity is based upon the direct interference with the circulation by the defect itself, and upon the well-known tendency of certain anomalies to become the seat of a future malignant endocarditis.

Among the least harmful forms of congenital cardiac disease may be mentioned anomalous septa in the auricles, and coarctation of the aorta with extensive collateral circulation, which may exist until past middle life without symptoms, frequently terminating then with a general failure of compensation under some undue strain upon the circulation. Patency of the ductus, too, is compatible with long life. Localized defects of the interauricular and interventricular septa belong likewise to the more innocent lesions, which may give rise to symptoms, or may be present indefinitely without producing any effect upon the circulation, becoming serious only upon the advent of some pulmonary complication raising the pressure in the right heart, or through the engrafting of a malignant endocarditis along the edges of the defects.

In the more complicated defects life is correspondingly shorter. Young's patient with cor biatriatum triloculare and anomalous septum attained the age of thirty-nine years, and Holmes' twenty-four years, but these are rare exceptions, the subjects of biloculate and triloculate heart usually dying in infancy. This is true also of persistent truncus arteriosus, although a patient reaching twelve years is recorded by Crisp. In pulmonary stenosis early adult life is not uncommonly attained, but is rarely passed, the patients dying as often of tuberculosis as of the direct effects of the lesion. Here again in exceptional cases life may be prolonged, Vulpian recording pulmonary stenosis, *rechtslage* of the aorta, and defect of the septum in a man who died at the age of fifty-two years. The average duration of pulmonary stenosis is given by Vierordt as 9.36 and of atresia as 3.27 years.

As graver conditions proving inevitably fatal during the first weeks or months of life may be enumerated: complete transposition of the arterial trunks without defect of the interventricular septum, pulmonary atresia with closed interventricular septum, tricuspid atresia, and last, but not least, aortic atresia, which is, indeed, the most serious of all, nearly all the cases recorded dying in the first two weeks of life, and many within a few hours of birth. The same is true of some forms of ectopia cordis, which are not viable. Finally, it is to be remembered that of the more complicated anomalies many must perish in the early stages of embryonic development, as only those in whom compensatory conditions arise survive until birth.

The prognosis depends chiefly upon the character of the lesion, which is often impossible to diagnose. For this reason symptoms will frequently prove a better guide to the immediate future than physical signs. Such conditions as septal defect, for instance, may give marked murmurs and thrill, yet lead to no hampering of the heart's action and to little interference with oxygenation. Persistent cyanosis, a continued low temperature, a marked increase in the number of red blood cells (above 5,500,000), and dilatation of the heart, all point to a grave disturbance of the circulation and to a rapidly fatal issue. On the other hand, the entire absence of cyanosis and its attendant phenomena does not always argue a favorable prognosis, for in such cases sudden death may occur without any

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warning, either quietly, or in a paroxysm of cyanosis with dyspnœa. As was said above, the embarrassment to the circulation which the lesion itself entails is not the only source of danger. Grave danger lies also in the frequent intercurrence of a malignant endocarditis, and in the fact that catarrhs, colds, and the more serious invasion of a bronchopneumonia are all apt to prove rapidly fatal. The liability of patients with pulmonary stenosis to tuberculosis, and the frequent termination by the sudden onset of cerebral complications, are other unfavorable factors. These considerations indicate the extreme gravity of the more pronounced cases, and the fact that even in the more innocent forms of congenital cardiac disease the prognosis must be framed with reserve and caution. Among the better class, where good hygiene prevails and the most suitable conditions of living can be sought, the outlook is of course better than among the children of the very poor.

Treatment.—This may be said to begin with the care of the mother during her pregnancy, for a study of the etiology clearly shows that to some unhealthy condition in the environment of the embryo or in the parental organism, rather than to an ancestral tendency toward anomalous growth, the majority of cardiac anomalies owe their origin.

The treatment of a patient suffering from congenital cardiac disease must be largely symptomatic or palliative, or directed to the preventing of complications. The indications here are to do all that is possible to facilitate the oxygenation of the blood, to avoid additional taxation of the already burdened circulation, and to shield the patient from those accidents or illnesses which will increase the pulmonary or systemic obstruction, remembering always that in the majority cyanosis first develops on the addition of some such factor to the pathological conditions produced by the lesion itself. A carefully regulated life, a plentiful supply of light, fresh air, and warmth, the maintenance of an equable bodily temperature, the avoidance of mental agitation and of undue physical exertion, rest, and quiet forms of exercise, where this last is permitted by the condition of the patient, are all essential. The diet should be carefully ordered, light and nutritious, and the often capricious appetite watched. Free action of the excretory organs, especially of the skin, should be promoted and the child kept clothed with flannel. Sudden changes in the external temperature must be avoided and, when possible, resort should be had to a warmer winter climate. Exposure to cold or wet, or to any of the causes of rheumatism, should be avoided on account of the great liability to acute endocarditis. When adult life is attained, choice of light employment which does not call for sudden or great physical exertion is important. In women child-bearing is fraught with danger.

Where cyanosis has developed, the administration of oxygen has been suggested as likely to be useful in relieving dyspnœa. Gibson, however, reports a negative result from its use in several cases. For the relief of the dyspnœic attacks diffusible stimulants, such as are used in angina, are of benefit and should be kept at hand; and in infants the hot mustard bath is useful. The frequent syncope may best be relieved by strychnine. Where failing compensation sets in, the usual treatment of rest and cardiac tonics is to be employed, and here strychnine is said to give better results than digitalis.

Thus, in a very few words, a careful hygiene and an expectant and preventive treatment may be summed up as the only available assistance that can be given. The condition does not admit of cure, but permits of amelioration and of arrest of the downward trend of the disease.

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CHAPTER X.

DISEASES OF THE ARTERIES.

By WILLIAM OSLER, M.D., F.R.S.

ACUTE ARTERITIS.

Mistaking staining of the intima for inflammation, the older writers described arteritis as a common event in many diseases. In the early years of the nineteenth century Cruveilhier and others believed that it was the cause of the clotting of the blood in the vessels, and that it arose spontaneously as a complication in the fevers. Virchow took an opposite view, viz., that the thrombosis was the primary event, and the arteritis always secondary, whether the clot was embolic in origin or formed at the site from conditions of the circulation or of the blood. Of late years we have learned to recognize that the arteritis is sometimes a sequel of the clotting, sometimes due to primary changes in the vessel wall.

Secondary Arteritis.—Secondary arteritis occurs when a local infection attacks the vessel wall from without, as in abscess formation, etc.; or when the intima is injured and inflamed as a result of an infected embolus or an infected marantic thrombus. This form will be considered in connection with embolism and thrombosis, in the course of which it is an incident.

Primary Arteritis.—Primary arteritis is a rare disease, met with as a complication in the acute infections, and occasionally as an independent malady. In ordinary medical work it is most frequently seen in typhoid fever, but its rarity may be judged of from the fact that in this disease there were only 5 instances in 1500 cases at the Johns Hopkins Hospital.[1] In smallpox, scarlet fever, influenza, and pneumonia, cases have been observed. It is less common in rheumatic fever, diphtheria, yellow fever, typhus, and measles. In typhoid fever, pneumonia, and diphtheria the organisms of the disease have been found in the vessel wall. In direct infection from the blood the intima is first involved, and there may be small vegetative outgrowths such as we see on the intima of the valves, but this is rare. In other cases the infection is conveyed through the vasa vasorum, and the adventitia and media are first involved. The grades of alteration in the vessel depend upon the type and virulence of the organism. The intima alone may be affected, with the result of the formation of a thrombus; in other cases the vessel wall is acutely inflamed and there are swelling and infiltration of the neighboring tissues.

Symptoms.—The symptoms depend upon the vessels affected. In the external arteries, as in the femorals or popliteals, there is pain, often of great

[1] Details of these are given in Thayer's Jerome Cochran Lecture, *Johns Hopkins Hospital Bulletin*, 1904.

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severity in the course of the vessel, spontaneous or on movement, and an increase in the fever with swelling over the vessel and sometimes redness. The pulse below is obliterated; the limb is at first pale and cold, and then gradually becomes livid at the periphery. When the femoral is obliterated, whether or not gangrene follows will depend upon the rapidity with which the vessel is blocked and the extent of the thrombus. There are cases which look threatening at first, and in a few days the signs of obstruction pass away. In other instances the process extends and both legs may become affected.

In the acute infections gangrene is only too apt to follow obstruction of the femoral artery. It is not always easy to determine whether the thrombosis results from a primary arteritis or an embolus. Suddenness of onset and the existence of conditions favorable to embolism point to the latter. There are cases in which the onset is severe, and for a few days the symptoms suggest that gangrene will follow, and then the circulation is reëstablished and color returns to the limb. Parietal thrombosis with only partial occlusion of the vessel may be present. Of our 2 cases of typhoid fever in which the femorals were affected, gangrene followed in one, in the other the condition cleared in a few days. In 1 case the brachial was involved at the bend of the elbow.

Arteritis of the internal vessels is still more rare. Of 2 of our cases in which the cerebral vessels were affected in typhoid fever, in 1 on the ninth day of the disease, in the other on the nineteenth, both proved fatal. In the arteries of the kidney, the spleen, and occasionally of the heart, a spontaneous clotting may occur as a result of inflammation in the acute infections.

Primary Multiple Arteritis.—There are instances in which in the course of a few days, without the existence of any local disease, a thromboarteritis occurs in many vessels, associated with high fever and signs of an acute infection. The writer has reported a remarkable case in a man, aged twenty years, who had had typhoid fever two years previously. He was admitted to the Philadelphia Hospital with fever, rapid pulse, diarrhœa and abdominal pain. He had thrombosis of both femorals and iliac arteries and of the lower two inches of the abdominal aorta, and of two large branches of the splenic artery. There were infarcts in the spleen and in the kidney.

Acute Aortitis.—Lesions of the aorta due to acute inflammation are exceedingly rare. The term aortitis has been used very loosely to describe conditions which are degenerative rather than inflammatory, and which come under the general category of arteriosclerosis. It is an altogether false conception of the process to speak of the degenerative plaques of the intima and the foci of medial necrosis met with so commonly in the infections as acute aortitis. The process occurs under the following conditions:

1. **Acute Vegetative Aortitis.**—In pneumonia, in rheumatic fever, and in the acute septic infections, the lining membrane of the arch may present numerous irregular vegetations identical with those on the valves. The condition is rarely if ever met with apart from aortic or mitral valvulitis. It is exceedingly rare, and the writer has not seen more than three or four instances. The outgrowths may be firm and warty in character, or a perfectly smooth intima may present a series of globose vegetations. Acute aneurism may be associated with the process. There may be half a dozen small sacs. Cases have been reported, particularly in France, in connection with rheumatic

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fever. Pneumococci and staphylococci have been found in the vegetations.

2. **Acute Mesaortitis.**—This is much more common, particularly in syphilis. Within a few weeks a localized productive aortitis occurs, largely confined to the media, but quickly involving the other coats, and leading to aneurism or to an acute dilatation of the part of the vessel affected, or to rupture with a dissecting aneurism. This is a type of aortic disease to which the term "acute aortitis" may very properly be applied, and will be dealt with under the subject of aneurism. Other varieties of acute infective mesaortitis are met with in pneumonia, rheumatic fever, and septicæmia. The infection is conveyed through the vasa vasorum and there are foci of softening, sometimes of acute suppuration, in the middle and outer walls of the artery. This may lead to localized weakening, so that the intima over the spot is split. As many as four, five, or six of these small fissures may be seen on the intima of the arch, each one leading into a little focus of softening and dilatation. Sometimes the edges of the splits are covered with luxuriant vegetations. Acute aneurism is apt to follow, which may rapidly prove fatal. To this condition, occurring in the course of an infection like rheumatic fever, the term "acute aortitis" is really applicable. There are instances in which in an aorta with perfectly smooth intima there is a small erosion like an acute ulcer, leading directly into an aneurism. The writer has reported a remarkable case, with the illustrations, in which in the lower part of a normal looking descending aorta there was a linear perforation 1.5 cms. in extent, which led directly into a small aneurismal sac which had ruptured into the œsophagus. The woman was only thirty-five. There was no endocarditis. The probability is that she had an acute mesaortitis comparable with that which may be produced in animals experimentally, and that over this small spot the intima fractured.

Symptoms.—The *symptoms* of acute aortitis are exceedingly vague. It is one of the most interesting points in comparative medical literature to read the extended description of the disease as given by French writers, and then to note the silence of American, English, and German authors on the subject. Except in syphilis, the writer has never made the diagnosis of acute aortitis; here the pain, often anginal in character, and the development, under observation, of aortic insufficiency, give decided indications of disease at the root of the aorta. In a case of acute rheumatic fever, or acute sepsis, signs indicating acute dilatation of the arch of the aorta would be suggestive. It must be borne in mind, however, that in a larger majority of cases of so-called aneurism occurring in children in connection with rheumatic fever, are instances of dynamic dilatation of the aortic arch in connection with aortic insufficiency. An abdominal aortitis is recognized by French writers, characterized by pain, throbbing, increased mobility, and a loud systolic murmur, with a relatively higher blood pressure in the femorals than normal. Clinically, the condition is quite as vague as the acute thoracic aortitis.

A special form, *tuberculous aortitis*, may be mentioned, of which a few cases have been described. In Flexner's case there was a small tuberculous nodule just below the left subclavian artery, seated directly on the intima, which everywhere else was smooth. Tubercle bacilli and giant cells were present and there were numerous tubercles in other organs.

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3. **Acute Peri-aortitis.** Occasionally in suppuration in the neighborhood of the aorta, as in connection with a lymph gland in the anterior mediastinum or in suppurative processes in the abdomen, the adventitia of the aorta may be involved, and presents a focus of suppurative softening.

CHRONIC ARTERITIS. ARTERIOSCLEROSIS.

Definition.—A general disease of the arteries, characterized in the small vessels by thickening of all the coats, and in the larger by gelatinous swelling, necrosis, fatty degeneration and calcification, the processes to which the name atheroma has been given.

Sometimes the term arteriosclerosis is limited to the smaller vessels, and that of atheroma to the larger arteries. On account of the irregularities due to calcification and atheromatous erosions, the name of endarteritis deformans is given to the process in the larger arteries.

History.—An excellent account is given of the coarser changes in the aorta and large vessels by Morgagni, who describes the gelatinous thickenings, the areas of atheromatous softening, and the ossification. He recognized the frequency of sudden death in disease of the aorta. Baillie figures the two chief lesions in his well-known *Atlas* (1799), the raised, irregular protuberances of the intima and the areas of calcification or ossification. The relation of changes in the coronary arteries to angina pectoris was studied by Jenner, Fothergill, and Parry. The relation of gangrene to blocking of the arteries was recognized by Boerhaave, Munro, and Meckel. The early writers of the nineteenth century paid special attention to disease of the arteries, and Hodgson's excellent monograph appeared in 1815. The illustrations in Cruveilhier's *Atlas* have never been excelled. Virchow's study of the disease, which he called *endarteritis deformans*, brought out its relation to strain, to increased pressure and to the toxic agents.

The modern view of arteriosclerosis as a general disease dates from the papers of Gull and Sutton (1872),[1] who called the process arteriocapillary fibrosis. Though in this paper they dealt particularly with the relation of contracted kidneys to arterial changes, in their first two conclusions they clearly announce a conception of arteriosclerosis which has undergone no essential change: (1) "There is a diseased state characterized by hyaline-fibroid formation in the arteries and capillaries; (2) this morbid change is attended with atrophy of the adjacent tissues." Sutton had an extraordinarily clear idea of the whole process and of the relation of visceral lesions to the vascular conditions. Thoma in his remarkable studies widened our conception of the pathology of the process, and he demonstrated that the thickenings and knob-like excrescences on the intima represented a compensatory process following disease of the middle coat. In injecting arteriosclerotic arteries with paraffin he found that the nodular projections of the intima were pressed back, making the inner surface level and smooth, while on cross-section, instead of a bulging of the intima there was a projection outward of the media. The recent histological studies which have so profoundly modified our views of the process cannot here be discussed. The monograph of Jores (1903) and the critical summaries in the *Ergebnisse* of Lubarsch and Ostertag (1904) may be consulted.

[1] *Medico-Chirurgical Transactions*, 1872, vol. lv, p. 273.

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The recognition of a separate type of chronic arterial disease due to syphilis, and its importance in connection with aneurism, has been brought out by the studies by Heiberg, and by Heller and his pupils. The syphilitic aortitis has special features which enable it to be recognized macroscopically and microscopically from the ordinary atheroma. Within the past few years the experimental production of arteriosclerosis has thrown a great deal of light upon the pathology of the process.

Etiology.—There are four great factors in the causation of arteriosclerosis—the normal wear and tear of life, the acute infections, the intoxications, and those combinations of circumstances which keep the blood tension high.

1. **Wear and Tear of Life.**—Among organs the bloodvessels alone enjoy no rest. Not only does a ceaseless rush of fluid pass through them at a speed of 10 inches a second, but the walls of the main pipe are subjected to a distending force of 2½ pounds to the square inch, 60 to 80 times a minute, 80,000 to 100,000 times in the twenty-four hours. The heart has rest in diastole, but distended by the charge from the left ventricle, the arteries pass it on partly by the natural elasticity of the walls, partly by an active contraction of the muscle fibers. Like other organs they live under three great laws—use maintains and in a measure sustains structure; overuse leads to degeneration; in time they grow old, in threescore or in fourscore years the limit of their endurance is reached and they wear out.

The stability of tubing of any sort depends on the structure and on the sort of material used; and so it is with the human tubing. With a poor variety of elastic and muscular fibers in the bloodvessels, some are unable to resist the wear and tear of everyday life, and have at forty years of age arteries as old as those of others at sixty. One day, at a meeting of the American Medical Association, Dr. Henry Martin (of vaccine fame), who possessed all histrionic gifts, demonstrating samples of Esmarch's bandages, one of which, as he spoke, he broke into fragments with great ease, while another resisted all his efforts. "They look the same," he said, "and they are made of the same substance, but they are not the same, one is shoddy, the other is the genuine article." And so it is with our arteries. They look the same macroscopically and microscopically, but they differ in different individuals in the quality of the materials used and the capacity to resist the ordinary stress of life. Not only are there individuals, but whole families with "shoddy" bloodvessels. Hence the truth of the old saying attributed to Cazalis, "a man is as old as his arteries." In the building of the human body, as of chaises, there is, as the Autocrat says, "always somewhere a weakest spot," and too frequently this is in the circulatory system.

The conditions of modern life favor arteriosclerosis, as a man is apt to work his body machine at high pressure, and often takes less care of it than of his motor. The best express engine from the Baldwin works run day by day at maximum speed will not last one-tenth of the time it would do if it were not so pushed. But nowadays, with the human engine it is top-speed or nothing, and we cannot wonder that it early shows signs of hard usage. In the fourth or fifth decade, even with the best of habits in eating and drinking, the incessant strain and anxiety of public life or of business may lead to degeneration of the bloodvessels. Mental exertion is not of itself injurious, and the life of the student need not be one of great tension, but the mental exertion of the modern business man is of a different kind. Com-

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petition is so keen and the environment so stimulating that, even without social or political ambitions, high pressure seems a necessity. The tragedies of life are largely arterial. Represented in the old mythology as winged, Nemesis, the goddess of the Inevitable, may still be pictured with a wheel, the wheel of life, to the ceaseless revolutions of which the circulation ministers. How often does her fatal touch call away in their prime the best and the bravest—men like the late William Pepper, whose only fault has been the unselfish abuse of the body machine!

After forty it is exceptional to examine the arteries without finding evidence of degeneration—here and there a small plaque of atheroma, an occasional streak of intimal fatty degeneration, and with this the mitral and aortic cusps may have lost just a little of their delicate tenuity. With advancing age the arteries become thicker and the atheromatous changes more marked. As a rule, in the very aged not only the smaller arteries are thickened, but the aorta and its main branches show extensive changes with calcification. Occasionally, however, a very old person may have singularly healthy bloodvessels. It is not the case, as so often quoted, that Harvey found the vessels of Parr, who lived to be one hundred and fifty-two (?), to be healthy. He does not mention them. Living quieter lives and with less stress and strain, women are not so frequently the subjects of arterial changes, and in consequence they last longer. In infants and young children arteriosclerosis occurs: (1) As occasional patches or flakes, or even calcified foci, in the vessels of the newborn. (2) In infants dying of the acute infections, streaks of fatty degeneration of the intima and foci of necrosis of the media are not uncommon. (3) Widespread arteriosclerosis of the smaller vessels may occur without nephritis and without recognizable cause. Two or three cases may occur in the same family. (4) In congenital syphilis, diffuse or localized sclerosis of the arteries may occur, sometimes early, sometimes as a late manifestation in *syphilis hereditaria tarda*. Fremont-Smith,[1] who has recently reviewed the literature of arteriosclerosis in the young, found no difficulty in collecting 144 cases.

2. **The Acute Infections.**—Of the acute infections, syphilis is the one with a special predilection for the arteries. There are changes best described as acute productive arteritis, and there are degenerative changes which come in the category of chronic arteritis. The special features of syphilitic aortitis will be described later. The lesion may be a chronic obliterative endarteritis, limited to a special group of vessels, as in the brain, the heart, or the vessels of the extremities. Extensive arteriosclerosis in infants and in children is very often syphilitic, and in the acquired disease a slow, progressive arteriosclerosis may exist in combination with other parasyphilitic manifestations. We have learned to recognize the great frequency in scarlet fever, measles, diphtheria, smallpox, and influenza, of foci of arterial degeneration. It has long been known that in typhoid fever areas of necrosis and fatty degeneration are met with in the aorta. The observations of Thayer[2] show how important are the cardiovascular relations of this disease. Of 52 postmortems at the Johns Hopkins Hospital, in which notes of the condition of the aorta were made, evidence of sclerosis were present in 30, and in 21 of these the changes looked recent. It is remarkable that out of 62 instances in which the condition

[1] *American Journal of the Medical Sciences*, 1908, cxxxv, p. 199.
[2] Jerome Cochran Lecture, *Johns Hopkins Hospital Bulletin*, October, 1904.

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of the coronary arteries was stated, in 19 sclerotic changes were present, and in 13 of these the changes were recent. One of our House Physicians, a very vigorous man of twenty-five, died at the end of the third week of typhoid fever. There were patches of endarteritis at the root of the aorta and numerous patches of yellowish sclerosis in both coronary branches. Thayer examined 189 patients who had had typhoid fever in the hospital within fourteen years, and 40 per cent. of the persons between the ages of ten and fifty presented palpable radial arteries compared with 17.5 per cent. of a series of control cases. The change may be in connection with the higher blood pressure which he found to prevail in these patients.

At the Franz-Joseph Hospital, Vienna, Wissal examined 300 bodies of children dead of acute infections, and in 80 found signs of arteriosclerosis, usually in the form of ordinary patches in the aorta and larger branches, but the small vessels were also found involved. It is interesting to note that he found the chief changes, which were in the media, to bear a striking resemblance to those produced in experimental aortitis in animals.

Tuberculosis is another disease with which arteriosclerosis is frequently associated. It has been observed by many writers that in chronic phthisis the superficial bloodvessels are apt to be thickened. It is rare to examine a patient with tuberculosis of the lungs of more than two or three years' standing without finding thickening of the superficial arteries.

Experimental production of arteriosclerosis by the various bacterial toxins afford an explanation of this gradual production of sclerosis in the chronic infections.

3. **Intoxications.**—Of the poisons which have an important influence on the bloodvessels, some are exogenous, others endogenous. Of the special exogenous poisons, alcohol, lead, and tobacco, the first named is very generally regarded as a potent influence in causing degeneration of the bloodvessels. In man it is very difficult to separate effects of alcohol from those of other causes. Of late years there has been a strong revolt against the popular belief. In France, Lancereaux rejects the evidence entirely. R. C. Cabot holds the same opinion, and it must be confessed that it is difficult in any given case to furnish evidence that alcohol alone is the cause. For example, in a middle-aged man who has drunk freely, eaten largely, and worked hard, it is impossible to say which of these factors is responsible for the degeneration of the bloodvessels. Alcohol may act either as a direct poison, causing necrosis of certain elements of the bloodvessels, or it may be a factor in maintaining a constant and high pressure.

Tobacco is another poison about which it is very difficult to get conclusive evidence. Experimentally, it is easy to produce the most extensive degeneration of the aorta in animals with nicotine. When one considers the extraordinary quantities consumed over long periods of years by men who show no trace of vascular change, or not more than the ordinary wear and tear of life would warrant, it is difficult to believe that tobacco can have a very important influence. It rapidly raises tension and may cause spasm of the arteries, which factor may account for the cases of sudden death in young or middle-aged men in whom excessive use of tobacco has been the only etiological factor. Angina pectoris is sometimes associated with abuse of tobacco, and the influence may be, as Huchard and others believe, through inducing an arteriosclerosis of the coronary arteries.

Lead has long been known to have a very important effect upon the

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bloodvessels. A slow, gradual sclerosis is common among painters and others who take a small quantity of lead into their system. There are three elements here to be considered: the direct toxic action of lead on the bloodvessels, the disturbance of metabolism which leads to gout, and the chronic interstitial nephritis, both of which are associated with high tension and favor sclerosis. Of other exogenous poisons, tea and coffee are supposed to have an influence, but it is not easy to get conclusive evidence of the connection.

Of endogenous poisons that may promote arteriosclerosis may be mentioned all the conditions of perverted metabolism, the hyperpyræmia of Francis Hare. The thickening of the arteries in gout, in diabetes, in chronic Bright's disease, in obesity, may be due to the action on the bloodvessels of poisons retained within the system.

4. **Conditions that Keep up High Blood Tension.**—The recent work of experimental arteriosclerosis, to be referred to later, shows the great importance of this factor in causing an arterial degeneration. Within limits, the pressure with which the blood circulates in the arteries varies very greatly, in order that the circulation may adapt itself to the varying conditions of life. Healthy individuals differ in the degree of the blood pressure, but one rarely finds it with the ordinary Riva-Rocci instrument above 150 mm. Hg. The pressure varies, too, at different periods of life, and as age advances the blood pressure rises. Sir Clifford Allbutt[1] has discussed this feature in a most suggestive paper. There can be no question that in many individuals the rise in pressure antedates the appearance of the arteriosclerosis. The following are some of the causes of this heightened blood pressure: (1) *Overeating:* Excess of food and drink acts in two ways, first by keeping the bloodvessels constantly distended, and secondly, in the processes of primary and secondary metabolism substances may be formed which are directly toxic. This is the condition which Francis Hare has very well described as *hyperpyræmia*, a state in which the system is damaged by products of imperfect metabolism. Of late years there has been a very general consensus of opinion on this point. The writer's attention has been repeatedly called to the frequency of arteriosclerosis in persons who have been temperate in every respect except at the table. It is well known to caterers that teetotallers eat much more than other people, and in the United States arteriosclerosis is very frequent among the well-to-do classes, who, as a rule, are abstemious so far as alcohol is concerned, but exceedingly careless and indulgent in the matter of eating. The writer's experience is fully in accord with that of Allbutt, that "one main cause of rising arterial pressure in middle life is excess of feeding, that is to say, of food in excess of work and excretion." The express engine capable of running fifty to sixty miles an hour if stoked for that purpose and put into the station yard to "shunt" empty cars will go to pieces very soon. This is what so many of us do with our engines. We supply the fuel for fifty miles an hour and run the engine at ten miles. In our bodies, as in the engine, damage is certain to follow from the accumulation of waste and the disproportion between intake, work done, and output. For the statement that meat eaters are more prone than others to arteriosclerosis we have no positive warrant, but the Indians and Japanese, who subsist chiefly on a vegetable diet, are said to be much less affected than Europeans.

[1] *Medico-Chirurgical Society's Transactions*, vol. lxxxvi.

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In no way is blood pressure more surely heightened than by the persistent use of the muscles. But here, too, we must be careful not to draw hasty conclusions. A majority of laboring men have the blood pressure from 30 to 50 or 60 mm. of Hg. above that of rest during the greater part of the day. This is well within the normal limits, and cannot be hurtful. It is the very severe muscular efforts repeated over prolonged periods that damage the cardiovascular system, the conditions that produce the hypertrophy of the heart, as in miners, mountain climbers, and athletes. The difficulty here is to separate the effect of muscular effort from associated conditions of overeating, alcohol, and tobacco. The possibility has to be considered of overactivity of the adrenals, a state of hyperepinephrism, in which an increase in the amount of the internal secretion, which keeps up vascular tone, causes hypertension and finally sclerosis. So far this is a purely hypothetical conception. Much light has been thrown upon the whole question by the recent studies on experimental arteriosclerosis.

Etiologically, then, there are three great groups of arteriosclerosis: first, the involutionary, in which the degeneration is caused by the ordinary wear and tear of life, and which is as natural as gray hair and failing eyesight; secondly, the toxic group, in which the degenerations are caused directly by the poisons of acute and chronic infections and of the intoxications; thirdly, the hyperpietic group, in which the degeneration follows persistent high arterial tension. Practically in a given case of arteriosclerosis, in a man of, say, fifty-five, two or all three of these factors may be present, and it is exceedingly difficult to assign to each their relative value.

Pathology.—It is rare to find the arteries entirely free from disease. Even in children small flecks of atheroma or fatty degeneration of the intima are by no means uncommon. In the bodies of middle-aged persons some arterial degeneration is always present, and, as a rule, the older the individual the more pronounced they are. In extreme old age calcification may be a widespread process, but occasionally the vessels of persons above eighty years of age show very little atheroma.

While arteriosclerosis is a general disease, affecting, as a rule, all of the arteries, the process may be much more advanced in some vessels than in others. The arteries of the brain may be stiff and hard, while those of the abdominal organs show no change; or the vessels of the limbs may be stiff and rigid, while the intima of the arch is smooth. The coronary arteries may be extensively diseased in comparatively young persons, while there are no changes in the other vessels. As a rule, this limitation of the disease to the vessels of one organ or to a limited portion of one of the large arteries, is characteristic of syphilis; but there are instances in which this disease can be excluded with reasonable certainty.

In the larger arteries, the aorta for example, the following are the important changes: (*a*) Small areas of fatty degeneration of the intima, of a yellowish color, not raised. This may be the only lesion present. (*b*) Gelatinous-looking raised areas scattered over the intima, and seen particularly about the orifices of the arteries. They are translucent, and on section are seen to be confined to the intima. (*c*) Larger plaques of yellowish color due to fusion and fatty degeneration of *b*. (*d*) Calcified plaques. (*e*) Areas of atheromatous softening, which may project above the level of the intima, and which the old writers called atheromatous pustules. (*f*) Open atheromatous ulcers, usually flat and due to the breaking down of

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foci of atheromatous softening. In advanced cases the inner surface of the aorta is rough and irregular from the presence of calcified plates and areas of softening. (*g*) On section of the vessel the changes are found to be chiefly in the intima, but the media is usually atrophied, sometimes with foci of necrosis and areas of calcification, sometimes of true ossification. The adventitia is thickened and indurated, but necrosis and calcification are rarely seen in it. In many instances we find all grades and phases of the process going on side by side. The artery may be dilated, and sometimes there are small aneurismal bulgings.

Experimental arteriosclerosis, which has been studied so carefully of late years by Jores, v. Gilbert and Lyon, Fischer, Pearce, Klotz, Harvey, and others, has thrown a great deal of light upon the mode of production of the disease. Inoculation with cultures may produce proliferative changes in the media with thickenings of the intima. Diphtheria toxin, on the other hand, causes degenerative lesions affecting chiefly the media and adventitia followed by calcification. The most remarkable degenerative changes follow the use of adrenalin and other agents which raise the blood pressure. Here the media is involved, necrosis of elastic and muscle fibers takes place, with fracture and splitting of the same with early calcification. Aneurisms are formed either by direct bulgings over areas of disease of the media or from splits of the intima.

Recent researches lead to the conclusion that in the ordinary type of arteriosclerosis the primary lesion is in the media, either productive or degenerative. To compensate, a reaction occurs in the intima with hyperplasia of the subendothelial connective tissue which undergoes hyaline, fatty, and calcareous changes. According to Thoma's view, this reaction of the intima is compensatory and adaptive, tending to strengthen the wall in the spots where it is weak and to restore the original lumen of the vessel.

Discussion is still active on the finer changes in the small vessels in arteriosclerosis. The controversies of the seventies, started by George Johnson, Gull and Sutton, Dickenson, and others, still rage. Where does the process begin? Is there a true hypertrophy of the muscle fibers? What is the relation of high tension (hyperpiesis) to the sclerosis? Which comes first? Is the primary mischief caused by the action of a toxin in the finer tissues of the capillaries and arteries? Or do these irritating substances cause spasm of the smaller vessels, and so raise the tension? What is the relation of the involutionary changes in the vessels in old age to those met with in younger persons? May not increased viscosity of the blood play an important role in causing high tension and arterial strain? We cannot say that any of these problems are finally settled, and the whole question is in the melting pot again in consequence of the remarkable studies on experimental arteriosclerosis. We lack definite knowledge of the finer changes in the capillaries, which are probably always involved (as Gull and Sutton believed), through which, after all, the essential processes of the circulation are carried on. As age advances the smaller vessels show definite changes, chiefly in thickening of the intima and moderate hypertrophy of the other coats. Later, degeneration occurs, fatty and necrotic, particularly in the muscle cells and in the elastic fibers of the media, and calcification is common. Alterations precisely similar to this physiological arteriosclerosis may be met with in young persons, even in children, and it is pathological only in the time of life at which it has occurred. Intimal thickening in which both the

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elastic and connective tissue elements are concerned is perhaps the most constant feature in all types of arteriosclerosis. It may be out of all proportion to the changes in the media, and may narrow or obliterate the lumen of the vessels—endarteritis obliterans. This is the most important single factor in the disease, responsible for more symptoms than all the other changes put together. It may be limited to one set of vessels, as of the legs or of the heart. The cause of this intimal thickening is much discussed. Thoma regards it as compensatory, particularly in the large vessels, but even in vessels the size of the ophthalmic artery he thinks it takes place to strengthen the vessel at a point weakened by disease of the media as illustrated in his well-known figure.[1] (See Fig. 45, p. 459.) The physiological intimal thickening as age advances is believed to strengthen the vessel weakened by senile changes in the elastic and muscular elements of the media, and in the pathological forms experimental evidence is in favor of this view.

The nature of the changes in the media and adventitia are much discussed. They probably differ in the different groups of cases. In the high tension—hyperpietic—form there appears to be an early hypertrophy of the muscular elements, as was so well described by George Johnson and more recently by Savill. It is not easy to determine this histologically, and the matter is still in dispute. The cut section of an artery contracted is very different in appearance from one relaxed, and appearances are very deceptive. This has been well pointed out by Arthur V. Meigs, whose figures of cross-sections of shrunken and unshrunken arteries show how different the coats look in the two states. In the involutionary and toxic forms, necrosis of the muscle fibers and elastic elements takes place with replacement by connective tissue, fat, or lime salts, very much as occurs in the larger vessels. The medial degeneration seems really as important in the small as in the larger arteries, and in the senile type the calcified beadings follow these necrotic changes.

Symptoms.—Arteriosclerosis disturbs function in three ways: (1) Following progressive arteriosclerosis the activity of an organ lessens and there is a gradual reduction in its capacity for work. The changes of senility are largely vascular. With a reduced blood supply the organs become less and less active, atrophy slowly but progressively comes on, and they become firmer and harder. In old age every organ and tissue in the body shows changes which may be attributed to progressive arteriosclerosis. (2) When the arteriosclerosis reaches a final and obliterative stage, if in an end vessel, necrosis follows in the territory supplied, or if, as so often happens, it is in the peripheral vessels of the foot or of the hand, gangrene supervenes. (3) Arteriosclerosis renders the small arteries more prone to spasm than normal vessels. The process may sometimes be studied in the vessels of the leg. The spasm is accompanied by pain, ischæmia, and loss of function. The diminished volume of the pulse is readily perceptible, the foot becomes pale, at the same time there is pain, and, if at all widespread, there is muscular disability. These attacks of angiospasm are not necessarily associated with sclerosis. They may occur in normal vessels, as, for example, in Raynaud's disease, which affords many opportunities to study the effects of spasm, not only in the vessels of the limbs, but the transient aphasia and the mono- and hemiplegic attacks of this affection are due to loss of function in consequence of spasm of cerebral vessels. As will be mentioned shortly,

[1] *Virchow's Archiv*, Band cxi.

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in speaking of the cerebral features, precisely similar attacks occur in arteriosclerosis which may be explained in the same way. These vascular crises have been introduced to do service in explanation of a whole series of phenomena, from lead colic to angina pectoris, and from cramp of the muscles to the gastric crisis of tabes. Pal, of Vienna, in his valuable monograph on *vascular crises*,[1] gives an excellent account of the whole condition. He refers to a case of great importance as illustrating the loss of function in a part caused by transient spasm. A man, aged sixty-three years, every day, or every few days, had blindness of the right eye, lasting from a minute to several hours. Wagermann, under whose care he was, found complete amaurosis with absence of pupil reaction. The ophthalmoscopic examination showed contraction of the retinal arteries and emptiness of the veins, appearances which passed off in a few minutes with restoration of normal vision.

In so widespread a disease the clinical features will depend upon the extent to which the process has involved the arteries of different organs. So remarkable are the powers of adaptation in the body that an extreme grade may be compatible with good health. It is an every-day experience to find arteriosclerosis in persons who look well, and who are able to perform the ordinary duties of life. Sudden death may be the first and only manifestation. Rupture of a bloodvessel in the brain, thrombosis of one of the coronary arteries, rupture of a small aneurism, acute dilatation of the heart—any one of these may carry off a man in whom there has never been any suspicion of an organic lesion. Natural death, euthanasia, comes through the bloodvessels. The description in Ecclesiastes of the gradual failure of the vital powers is an epitome of the clinical features of senile arteriosclerosis. The symptoms are as varied as the organs involved. But before entering into consideration of the special features, it may be well to consider arteriosclerosis as a—

General Disease.—As already stated, there may be no symptoms of ill health, and the condition may be met with in a casual examination, as for life insurance. In a man who has led a very energetic life, particularly if he has worked hard with his muscles, eaten much, and drunk hard, the palpable arteries are felt to be thickened, the blood pressure is heightened, there is an increase in the vigor of the cardiac impulse, the apex beat is a little dislocated outward, the first sound is thudding and prolonged, and the second is accentuated. Such a patient may look a very robust man. When present under the fortieth year, such features are always of serious, although not always of immediate significance, and it does not do to give, as is sometimes done, a too unfavorable prognosis. Mental and bodily vigor of exceptional degree may persist with the most pronounced arteriosclerosis. The discovery may be a most advantageous thing, as the patient may be warned to change his method of life. A man who has been racing like the Lusitania, and in constant hazard of a breakdown, may be able to keep up indefinitely when the pace is reduced to ten knots an hour. An early symptom of the general disease is a slight pallor, all the more noticeable if the individual has had previously a high color. With it there may be no actual reduction in the number of red blood corpuscles. It is a question altogether of local anæmia. A gradual loss of intellectual and bodily vigor is the most striking symptom. Within a few years a man may, as we say, age visibly and lose his intellectual

[1] *Gefasskrisen*, Leipsic, 1905.

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keenness. The muscular energy is lessened and he is prematurely senile. Often the skin gets flabby and lax and the hair turns gray early. The condition is best expressed in those well-known lines of Oliver Wendell Holmes, describing the One Hoss Shay on the morning of its one hundredth anniversary:

"A general flavor of mild decay,
But nothing local. . . ."

And as in that venerable vehicle the breakdown is apt to be sudden and general. Slowly advancing, the peripheral arteries harden, the retinal vessels become more tortuous, the blood pressure rises to 150 to 200 mm. Hg., the cardiac hypertrophy becomes more marked, and the urine shows a slight amount of albumin and tube casts. Even at this stage the conditions may have been met with accidentally and the patient may be quite able to attend to his business, although conscious of failure in capacity. Very many of these patients, particularly under forty years, come to us with symptoms of neurasthenia, irritable, sleepless, and emotional.

Local Manifestations.—Nervous System.—As just mentioned, the patient may present quite early all the complex and varied manifestations of neurasthenia. In the more advanced stages of the disease the cerebrospinal features are among the most important and interesting. Headache is an early and distressing symptom, associated, as a rule, with high pressure and often promptly relieved by measures which reduce it. Usually frontal and continuous, occasionally paroxysmal and resembling migraine, many patients first consult a physician for it and the real cause may be overlooked, unless careful examination is made.

Vertigo.—Transient giddiness is a very common symptom and may be one of the most distressing, although it is usually quite temporary and never with the severity or associated features of Ménière's disease. It may, however, be associated with tinnitus. It is often brought on by exertion, or follows a sudden movement, and is an accompaniment of the crises of hypertension to which some patients are subject.

Transient Monoplegias, Aphasia, and Paraplegia.—One of the extraordinary cerebrospinal manifestations of the disease is the occurrence of attacks of transitory disturbance of function of parts of the brain or of the cord, leading to hemiplegia, monoplegia, aphasia, or even paraplegia. Years ago the writer's attention was called to these occurrences in the case of a friend and colleague, a man of about forty years, with extreme arteriosclerosis. After an attack of slight palpitation of the heart, with shortness of breath, he awoke one morning to find himself unable to speak or to use his right hand. The paralysis passed away in the course of twenty-four hours, and he regained the power of speech a little more slowly. He had a dozen or more of these transient attacks lasting a little longer than others, but with recovery so complete that he was able to resume his work. Once there was transient paraplegia, and for more than two days he was unable to walk. Headache was variable, not always present. The writer has seen a great many cases since, and has come to recognize it as a not very uncommon feature in arteriosclerosis of the cerebral vessels. The attacks are sudden and the recovery is complete. One patient had, within two years, at least twenty attacks of transient paralysis, sometimes on one side, sometimes on the other. Although not so widely recognized as it should be, the condition has been described by many writers, particularly Peabody, Edgeworth, and

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others. The transitory nature, with complete recovery and the extraordinary frequency of the recurrence, put hemorrhage, embolism, and thrombosis out of the question, and the condition must be an angiospasm similar to that which produces manifestations of Raynaud's disease.

Convulsions of an epileptiform character may occur. In the absence of syphilis and of lead poisoning, convulsions occurring in middle-aged individuals should always excite the suspicion of arteriosclerosis. They are associated with high pressure, sometimes very high, and are often preceded by headache and giddiness. In Stokes-Adams disease the convulsions are attributed by some to angiospasm and arteriosclerosis of the cerebral vessels.

Progressive Dementia.—Gradual failure of the mental powers is one of the commonest symptoms of cerebral arteriosclerosis. A man begins to take less interest in his affairs, grows careless and apathetic, the memory and judgment are at fault, the facial expression is dull, and, progressing month by month, at last the psychical powers are so reduced that the individual is in a state of dementia. Apart from syphilis, in which the dementia has the well-known features of paresis, mental degeneration is not often seen as a result of arteriosclerosis in men under forty years. It is common enough as a pre-senile change in men at or about sixty years. It may be associated, too, with periods of excitement and with mental vagaries of all sorts. Rupture of the cerebral arteries leading to apoplexy and thrombosis in consequence of changes in the intima are common events in arteriosclerosis.

Cardiac.—There are three important groups of cases in which the dominant symptoms of arteriosclerosis arise from affection of the heart—the valvular, the myocardial, and the coronary.

Valvular Group.—In a considerable number of aortic and mitral valve lesions the insufficiency is due to a process in the segments identical with that which goes on in the vessels. The former is a much more important group than the latter, and a considerable proportion of all cases of aortic insufficiency in men belong to it. These forms will be considered in the section on valvular disease of the heart.

Myocardial.—In general arteriosclerosis gradual failure of the hypertrophied cardiac muscle is a common and serious event, leading to the characteristic clinical picture of dilatation and progressive asystole. After a period in which the patient suffers with palpitation or violent action of the heart, he begins to get short of breath and is winded quickly by the stairs or by a slight hill. He may awaken at night in a slight paroxysm of dyspnœa. At this period examination may show a forcible apex beat and a high-tension pulse. An attack of angina pectoris or of pulmonary œdema may occur. Soon the dyspnœa increases and the patient feels that his disability is altogether respiratory, and that if he could only get his breath he would be all right. The signs of dilatation of the heart become more marked, and there is a characteristic picture of asystole, orthopnœa, slight swelling of the feet, and cough, with, perhaps, blood-stained expectoration. The pulse is often at this stage very deceptive, as it is not always weak. The apex beat is diffuse, undulatory on palpation, and one may feel a gallop rhythm, while over the whole heart the gallop rhythm is heard on auscultation. There may be an associated systolic murmur, and the aortic second sound may still be ringing or even amphoric in tone. The state of the urine depends entirely upon the degree of venous congestion. With judicious treatment the condition may be relieved in a week or ten days, and the patient may be able

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to resume work. A dozen or more of such attacks may follow before the patient succumbs. Even after months of dyspnœa and asystole, recovery may take place.

Coronary Arteries.—The orifices, the main branches, or the smaller vessels may be affected. The narrowing of the orifices is a common cause of myocardial degeneration and weakness, and in young syphilitic subjects, of attacks of angina. The same may happen in any case in which the sclerosis is advanced at the root of the aorta and the orifices of the coronary arteries are seriously narrowed. Involvement of the main branches produces the same condition, but attacks of angina pectoris are more common and in a large group of cases sudden death occurs from thrombosis in one or other of the branches. In many instances of arteriosclerosis in comparatively young men the coronary arteries are involved out of all proportion to the other vessels and the attacks of myocardial weakness may precede or accompany angina pectoris, or one may be surprised to find, in a case of sudden death in a middle-aged man, who has never had any cardiac symptoms, that there is gradual fibrosis or perhaps areas of anæmic necrosis are present with softening and occasionally rupture.

Renal.—There are two great groups of cases: (*a*) associated with the small contracted kidney, following an acute nephritis or coming on insidiously in gout or chronic lead poisoning, there is an extreme grade of arteriosclerosis which may be regarded as secondary and due partly to the high pressure and partly to toxæmia; (*b*) the true arteriosclerotic kidney is a red, beefy organ which is firm, hard, and dark in color, not at first reduced in size, sometimes, indeed, slightly enlarged. Very often, with this kidney, there may be few or no urinary symptoms. In a late stage there may be large, flat areas of atrophy of the cortex, or a large section of one organ may be involved in consequence of an obliteration of the arteries passing to the part.

The urine in these two groups of cases present, as a rule, striking differences. In the small contracted kidney the amount is increased, the specific gravity is very low, the albumin small in amount, often absent in the morning, hyaline casts are present, and very often red blood corpuscles. The urine of the arteriosclerotic kidney may contain at first no albumin, or, if present, the amount is not large, the specific gravity is normal or sometimes high. Later, the albumin may be large in amount and sometimes, as when a patient is admitted with an attack of cardiac dilatation, the urine is scanty with large amount of albumin and numerous tube casts, due to an acute intercurrent nephritis.

Abdominal.—Much attention has been paid of late years to abdominal symptoms in arteriosclerosis. Pal and others believe that very many of the painful gastric and intestinal conditions are associated with spasm in the gastric and mesenteric vessels; some would associate the multiple functional disturbances of abdominal neurasthenia with degenerative changes in the arteries. Certainly one may see a sclerosis of the mesenteric vessels far in advance of that in other vascular territories, but the writer does not know that we are yet in a position to say that any definite symptoms are connected with it. Ulcer has been met with in connection with endarteritis of the smaller vessels of the stomach. The victims of angina pectoris may have marked abdominal symptoms, and of late writers have spoken of such attacks of abdominal pain as *angina abdominis*. This is really an old story, as years ago Leared described "a disguised disease in which the heart affection was so masked

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by that of the stomach that nothing in the statements of the patient had any bearing on the primary disease." A number of these cases have come under my observation, but even when the pain is entirely abdominal the general features have usually been sufficient to make a diagnosis.

Milder attacks of epigastric pain and intestinal cramp and meteorismus have been attributed to arteriosclerosis. The clinical features of gastric and intestinal dyspnœa have been regarded as manifestations of circulatory disturbance in the sclerotic vessels. One cannot read the literature on the subject that has appeared of late without feeling that the writers have often been carried away with theoretical considerations. An intermittent claudication of the stomach has been described.

Peripheral Arteries.—A few among the many manifestations following sclerosis of the arteries of the limbs may be considered:

Cramps of the Muscles.—Local tetanus (cramp) in a muscle follows overexertion or a sudden prolonged effort in a strained or unaccustomed position. Long-distance runners are very subject to cramp in the calves of the legs, and sustained use of any group of muscles may throw not the whole group, but some portion, into strong tetanic cramp. This form and the commoner variety, which results from strained posture, are met with in young and old, but in the latter there is a form of great interest, and often very troublesome, which is probably associated with arteriosclerosis. Few elderly persons escape attacks of cramp, chiefly nocturnal and sometimes of such severity that the condition requires treatment. It is more common in persons of full habit and of what we call a gouty disposition—*i. e.*, persons who eat too much and work too little; but attacks may occur in thin, abstemious persons. It is difficult to connect the condition definitely with angiospasm, but the writer has so often found marked sclerosis of the palpable vessels of the legs, or absence of the pulse in the dorsal arteries of the feet, that he has come to regard the bad nocturnal attacks in elderly persons as a manifestation of endarteritis. Twice attacks of the most dreadful agony have been seen, recurring every few minutes in the muscles of the legs, knotting them in places into hard lumps which took a minute or two to disappear. In one old woman they were so severe that only large doses of opium gave relief. In both these patients the pulse could not be felt in the feet. Ligation of an artery may throw the muscles into a spasm, and the sudden tap on the facial artery may cause tetany of the muscles, so that it is not impossible that angiospasm (a vascular crisis) may be responsible for these painful cramps in elderly persons.

Neuritic Pains—Erythromelalgia.—In connection with endarteritis obliterans of the vessels of the legs, numbness, tingling, burning, and shooting pains are common complaints. In diabetes a whole group of neuritic symptoms may precede the local gangrene of the toes, and the same may occur before senile gangrene. In erythromelalgia, the red painful neuralgia, arteritis obliterans has been found in many cases. And there is a very interesting group of cases of idiopathic endarteritis of the vessels of the legs, in which in comparatively young men, without any history of syphilis, pains precede the occurrence of the severe obstructive manifestations.

Intermittent Claudication.—In the cases in the horse, described by Bouley, and in Charcot's original case in man, the vascular obstruction was aneurismal. To Erb we owe the recognition of the frequency of this symptom in arteriosclerosis of the vessels of the legs. It is a question of a due balance

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between a supply of energy through the blood and muscular expenditure, as Allan Burns puts it in his original explanation (1809). There are cases with neuritic pains and well-marked signs of vascular disease, palpable vessels, spasm of the arteries, with pallor of the feet in exertion, or absence of pulsation in the dorsal arteries of the feet. In others, the signs of arterial disease are not so clear, and it is possible that there may be an angiospastic form; or it may be in some cases, as Déjérine suggests, an affair of the spinal arteries with anæmia of the cord. In the majority of the cases seen by the writer, the arteriosclerosis has been pronounced. It is not always a cramp-like pain that causes the limping or claudication, but there may be a relaxation of the limbs, a giving way for a few seconds, or, without actual falling, an inability to make any further effort. The relation of arteriosclerosis to the peripheral arteries, to gangrene, erythromelalgia, scleroderma, etc., will be considered in other sections.

Diagnosis.—To the rule that the disease is uniformly distributed in the body there are many exceptions. The most widespread peripheral arteriosclerosis may exist with a moderate grade of disease of the aorta. On the other hand, the endarteritis deformans of the latter vessel may be out of all proportion to the disease in the smaller arteries. The vessels of the head, of the heart, or of the kidneys may be in an advanced stage of sclerosis, without any change in the palpable arteries. The most serious form is that in which the smaller vessels are chiefly affected and which comes on in middle life or in young persons.

From the appearance of the individual not much may be determined. To no condition is Shakespeare's remark more applicable—"the outward shows may be least themselves." A robust, vigorous looking man in the prime of life may have vessels in the most advanced stage of sclerosis. While there are patients who present a pronounced anæmia, the florid cardiovascular facies is the more common. The active muscular business man of forty-five years, who all his life has never had to spare himself, and who has prided himself on his "fitness" for everything, is shocked to find that there is something wrong with the machine; or to the young-old man who has reached the grand climacteric without a day's illness, Nemesis whispers "time is up." In other instances a remarkable change takes place in a few months. Following, perhaps, a domestic shock or a financial crisis, in other instances without any obvious cause, a man begins to fail. The elasticity and firmness go from the gait, the movements become less active, there is loss in weight, and the intellect is impaired, as shown in absence of initiative and in capacity for continuous work. So rapid may be the breakdown that some of these instances of pre-senile arteriosclerosis may be termed acute. Too much stress must not be laid upon certain features usually regarded as indicative of degeneration. Early graying of the hair may have nothing whatever to do with arteriosclerosis, and in my experience it has not been a common accompaniment. Nor is the arcus senilis of much value as an indication. It may occur in middle-aged men with perfectly good arteries, and it has not been in my experience a special feature in early arteriosclerosis.

The cardinal points in a case of arteriosclerosis are usually well marked: (1) thickening of the peripheral vessels; (2) signs of hypertrophy of the left ventricle, shown by the apex beat dislocated outward, the thudding first sound, and the accentuated aortic second; (3) heightened blood pressure;

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(4) a slight and variable amount of albumin in the urine. As a rule, this quartet of symptoms is present in a large proportion of the patients when first they come under our observation. At this stage the damage is done. The important point for the practitioner is to learn to recognize the early stages, when there is a reasonable chance that the progress may be arrested. We can form a pretty clear judgment of the state of the arteries and the general physics of the circulation by sight, by touch, by estimation of the blood pressure, and by the study of the pulse.

When at all advanced, the superficial arteries of the body become visible and tortuous. This is particularly well seen in the temporals, which, as age advances, stand out as prominent, tortuous, even beaded cords. One must learn not to mistake a full for a sclerotic vessel. When the peripheral circulation is relaxed, as in high external temperatures or during excitement, the superficial arteries become prominent. When the sclerosis is at all advanced the brachials stand out markedly sinuous and throbbing visibly. The radials and ulnars, the external iliac just above Poupart's ligament, the femorals just below, and the dorsal arteries of the feet may all be visible. Of all vessels in which to see early thickening, the retinal arteries are the most important. de Schweinitz in particular has called attention to the great importance of its early recognition by the ophthalmoscope. Not only may it be readily seen that the arteries are thicker than normal and more tortuous, but the way in which they cut across the larger veins is very distinctive.

By palpation we are enabled to judge with fair accuracy of the degree of thickening of the vessel wall. It requires not only experience, but education, to form a correct judgment on the state of the arteries. A perfectly normal vessel, when contracted, may feel hard and cord-like. On the other hand, in a radial definitely thickened, but in a state of extreme relaxation, the hardening of the walls may escape detection. The state of the tissues about the artery, the amount of fat in the skin, the size and fulness of the veins—all have to be considered. One of the commonest of mistakes is to regard as thickened any vessel one can roll under the finger. But in a state of very high tension and if very full, the arterial tube may feel cord-like. To estimate the presence of sclerosis it is not sufficient to examine the radials and temporals, but the brachials and femorals should also be felt, and palpation should be made, first, in the natural condition; secondly, the artery should be felt below a point where the pulse wave is obliterated; and thirdly, a small section of the vessel should be emptied of blood and palpation made between the two points of pressure. It may only be in this last way that a true opinion can be formed of the existence of sclerosis. It does not do simply to obliterate the pulse and feel immediately below it, because in conditions of very high tension, in the radial and temporal arteries for example, the recurring pulse appears beyond the point of pressure. In the superficial arteries, as the radial, the finger is able to appreciate four distinct grades: (1) the normal vessel wall, which in a moderately thin wrist may be just differentiated from the adjacent tissues; in the cold, or if the hand has been placed in ice-cold water the tightly contracted artery may be felt as a fine cord; (2) moderate sclerosis in which the vessel is readily felt and in which, after the blood has been pressed out of the artery, there is a definite tubular cord; (3) extreme sclerosis in which the radial is felt like a piece of whipcord, firm, hard, incompressible, rolling under the finger, and presenting little or no difference in

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the sensation with the blood in or out of the vessel; (4) calcification, which in the radial is easily felt, ringed or beaded.

The introduction of late years of clinical instruments for measuring blood pressure has given us one important means of estimating accurately the condition of a subject of arteriosclerosis. Early in the disease, or before the thickening of the vessel is evident, the blood pressure may be persistently high. This pre-sclerotic stage, as it has been called, is important to recognize, and yet it is only exceptionally that we are able to trace all the stages in a given patient. More commonly the high pressure and sclerosis are co-existent, but there is no definite parallel between the two processes. The very highest pressures, above 250 mm. Hg., may be present with quite moderate thickening of the vessels. On the other hand, low blood pressures may co-exist with early arteriosclerosis, or following an acute illness, dilatation of the heart, a shock, or certain complications, such as pulmonary œdema, and in the late stages of the intercurrent affections.

The character of the pulse in arteriosclerosis is best described as hard and resistant, and the vessel is plainly perceptible to the finger in the intervals of the beats. As already mentioned, it is important to recognize the difference between the hard sensation conveyed to the finger by a high-tension pulse and that conveyed by stiffening of the walls. The two may co-exist, but the former may give the deceptive sensation of a permanent cord to the artery. Usually, too, the pulse is incompressible, or, more correctly, is difficult to compress. One can always obliterate the pulse wave in the radial, but it quite commonly happens that, in spite of the firmest pressure, the pulsation may be felt beyond the finger. This is a recurrent pulse through the superficialis volæ, and it may be at once checked by compressing the ulnar artery. It is present frequently in high tension, but it is just as common when the smaller arterioles are greatly relaxed and the peripheral tension low. To estimate the state of the vessel wall in a high-tension pulse, obliterate the radial artery close to the metacarpal bone, then with the index finger of the other hand press the blood out of a section of the radial, compress it, and then, with the middle finger, feel the empty vessel. If very sclerotic, it will be almost as prominent empty as full. But when the cord-like sensation is due to a high pressure only, there may be very little sensation given to the finger by the vessel wall itself. The sphygmographic tracing of the high-tension pulse is very characteristic, with a wave of moderate height, a sloping ascent, and a delayed decline with a little or no dicrotic wave.

Treatment.—Once degeneration, fibrosis, and calcification have taken place, the damage is irreparable, and as "all the King's horses and all the King's men could not put Humpty Dumpty up" after his fall, so all the hygienic, dietetic, and medicinal measures cannot restore the normal structure of the arteries. But this does not mean that the condition is always hopeless. Much may be done to prevent the sclerosis increasing and much may be done to relieve symptoms.

The treatment may be carried out along the following lines, varying, of course, with the individual cases:

General.—The patient should be urged to live as peaceful a life as possible, cutting off all sources of mental strain and worry. A protracted holiday may be most helpful. It is not wise, as a rule, to urge a man to give up work entirely. Too often this is followed by a neurasthenic breakdown. The most difficult part of the treatment is so to arrange a man's life that he

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may have moderation in work. So long as it can be lightened, there is no reason why he should not continue. Of course, when there are signs of cardiac failure or any pronounced local features, or if the mental changes are marked, it would be wise to urge complete rest. These patients often require the consolation of sensible advice. On hearing that they have hardening of the arteries, many men with years of useful life before them are inclined to throw up the sponge at once. When of moderate extent in a man aged forty-five or fifty years, it may not lessen the expectation of life by more than five or six years. The writer has several arteriosclerotic friends in whom the condition was recognized more than twenty years ago. One old patient, who returned from a visit to London in 1881, was prepared to give up everything because of his arteriocapillary fibrosis. The fright was the best thing that ever happened to him, as he lowered sail and has been going on very comfortably for twenty-six years and doing a fair amount of work.

Exercise.—Golf, horseback riding, walking, bicycling, all in moderation, are advantageous. Allbutt recommends cautious hill climbing. The relaxation of the vessels of the skin and of the peripheral arteries generally which follows moderate exercise lowers the blood tension and relieves the heart. All sudden effort likely to throw a strain upon the vessels should be avoided. The action of the skin should be promoted by a daily bath. In the winter it is best taken at night and warm. An occasional Turkish bath, with a good rub, is helpful.

Food.—The one essential factor in the diet of arteriosclerotic patients is reduction in the amount. He should be taught gradually to reduce the quantity of food until he finds the minimum on which he can maintain the mental and bodily vigor. He will often be surprised to find that it is one-third or one-fourth of that which he has been in the habit of taking. He may take a cup of tea, a boiled egg, and a couple of slices of toast for breakfast; a vegetable soup with a rice pudding for luncheon; a piece of fish, a couple of vegetables, and stewed fruit for dinner, with a glass of hot milk at night, or a bowl of bread and milk. With a diet along these lines an arteriosclerotic may successfully pray the prayer of Hezekiah, and get, like him, a fifteen years' extension. He can do without meat perfectly well. Oysters, eggs in moderation, and fish may be taken with plenty of fruit, vegetables, plenty of bread and butter, and milk. It does not seem that we need dread specially the injurious effects of the lime salts which are abundant in milk and in eggs. Buttermilk is an excellent and easily digested food, even when milk is not. Sour milk has been a favorite drink with many persons who have lived to a very advanced age, like Thomas Parr, and in this connection it is interesting to note the strong opinion of Metchnikoff as to the value of the lactic acid products in preventing abnormal processes of fermentation in the large intestine. Spirits of all sorts should be given up. Tea and coffee may be taken in moderation. A man who has been a heavy smoker should reduce his allowance to two or three cigars a day.

Medicinal Treatment.—Of remedies believed to have an influence directly upon the coats of the vessel, only iodide of potassium is of value. It is stated that, experimentally, arteriosclerosis may be prevented if, coincidently with adrenalin, iodide of potassium is given to the animal. In all syphilitic cases it should be used freely, and even in others in the early stages the drug should be administered in moderate doses, 15 to 20 grains (gm. 1 to 1.3) three times a day, and kept up for some months. It is believed by some that

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the iodide of potassium lessens the viscosity of the blood, and in this way lessens the work of the heart.

The blood pressure is much more efficiently lowered by dieting and mode of life than in any other way. Of the drugs which have an influence, the nitrites are the most important. The commonly used nitroglycerin is often effective, but rarely given in large enough doses, and even then is apt to be very transient in its effect. It is best given in solution freshly made, and the patient may take from 1 to 3, 4, or 5 minims of the 1 per cent. solution three or four times a day. In crises of high tension larger doses may be given. It does not seem to do any harm, and individuals react so differently to the drug, that it is well always to test it upon each patient. We often do not get good results until much larger doses are given than those usually employed. The sodium nitrite, in 1 to 4 grain (gm. 0.06 to 0.25) doses every three or four hours, has a somewhat more permanent action and is often of very great service.

On the view that in arteriosclerosis the blood is poor in certain salts, various mixtures have been recommended, such as Trunecek serum, which is a mixture of the various salts of the blood in about the proportion contained in the serum. They are also prepared in tablets by various firms as antisklerosin tablets. Arsenic in small doses is helpful, particularly in the cases with early anæmia. One difficulty which everyone has experienced is to keep the blood pressure low by means of drugs; the reduction is temporary, and very soon the instrument records pressures as high as ever. In the crises of hypertension brisk saline cathartics are most helpful. In any case it is well to bear in mind that the only valuable measures for permanent reduction of blood pressure are the hygienic and dietetic. The treatment of the various complications of arteriosclerosis are dealt with in the other sections of diseases of the heart, kidneys, etc.

POLYARTERITIS ACUTA NODOSA (PERIARTERITIS NODOSA).

In 1866, Kussmaul and Maier reported a case of a man, aged twenty-seven years, who had an acute, progressive "chlorotic marasmus" with fever and tenderness of the skin and muscles. Hard, bead-like nodules were present in the skin of the thorax and abdomen, which were afterward found to be thickening of the subcutaneous arteries. The case was thought to be one of trichinosis. Postmortem, little aneurisms were found on almost all of the smaller arteries of the body. These were believed to be due to inflammatory infiltration of the adventitia, and they gave the name *periarteritis nodosa*. Since then there have been sixteen or nineteen cases recorded. A full abstract of each is given by Dickson in his recent paper.[1] Only three of the patients were females. The arteries of the heart, the kidneys, mesentery, and the liver were attacked in all the cases. The physical features depend a good deal upon the vessels affected. The onset is, as a rule, sudden and there is moderate fever throughout. Weakness, hyperæsthesia, pains in the muscles, anæsthesia, and anæmia are marked symptoms. Vomiting and diarrhœa are common. Headache, excitement, convulsions, optic neuritis, and paralysis may be present when the cerebral vessels are involved.

[1] *Journal of Pathology*, 1907, xii, No. 1.

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The diagnosis has rarely been made; the condition is usually mistaken for meningitis or typhoid fever. A remarkable case was admitted to my ward in 1901, and is reported by Sabin:[1] The patient was a woman, aged thirty-two years, who had had dilatation and vomiting with emaciation and anæsthesia; she looked very ill and had been confined to bed for five weeks. There was an extreme grade of annular sclerosis of the arteries, numerous subcutaneous hard nodules were scattered over the abdomen, just such as were present in the case of Kussmaul and Maier. The case was very similar in many respects to the one reported by H. M. Fletcher.

Nothing is known as to the etiology of the disease. Bacteria have not been found. The earliest lesion apparently is a destruction of the muscular coat with the giving way of the internal elastic lamina of adventitia leading to aneurismal dilatation. Dickson thinks that there is a primary periarteritis established, involving the vasa vasorum. The little nodular bodies may be present in enormous numbers. Many of the little aneurisms are filled with thrombi. The condition differs entirely and must be distinguished from nodular periarteritis of syphilis.

[1] *Johns Hopkins Hospital Bulletin*, 1901, xii, p. 195.

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CHAPTER XI.

ANEURISM.

By WILLIAM OSLER, M.D., F.R.S.

Definition.—A tumor containing blood in direct connection with the cavity of the heart, the surface of a valve, or the lumen of an artery.[1]

History.—Galen, the first author in antiquity to deal with aneurism, recognized two forms, one from dilatation, the other from the wounding of a vessel. In the former the tumor was deeply seated, and when pressed upon by the fingers a "sort of noise" was heard; in the latter the aneurism was rounded and felt more superficial. He knew that aneurism might follow a wound of an artery in performing venesection. A young and unskilled doctor opened the artery for the vein at the bend of the elbow. Galen cured it by the application of a sponge with bandages (*Methodus Medendi*, Liber V, folio LXIII, Linacre's edition, 1519). Of the men in antiquity who wrote on aneurism, Antyllus, the surgeon, who lived about the middle of the second century A. D., is the most interesting. Like Galen, he recognized that "there are two kinds of aneurism, the one arising from a local dilatation of the artery, . . . the second sort arising through rupture of the vessel, and the blood is poured out into the surrounding soft parts." He knew that it was dangerous to operate on the larger aneurisms in the neck and the axilla, but for the smaller sacs in the peripheral vessels he devised the operation which bears his name, and which consisted in ligating the artery above and below, opening the sac and clearing out its contents. From a remark which he makes we may gather that some of his contemporaries did the modern operation of extirpation of the sac which Antyllus thought too dangerous. Not much of additional value about aneurism is to be found in the ancient writers. The Arabians, who followed Antyllus in their method of operation, were familiar with the aneurism following venesection, and knew that it was associated with a hissing sound on palpation. Nor did the surgeons of the thirteenth, fourteenth, and fifteenth centuries—Lanfranc, De Mondeville, Guy de Chauliac—make any notable improvements. It was not until the sixteenth century that an advance was made by the recognition of aneurism of the internal arteries. Fernelius says that "aneurism likewise happens sometimes in the internal arteries, especially under the breast, about the spleen and mesentery, where a vehement pulsation is often observed" (Pathologia, i, 5, c. 12). Vesalius was the first to diagnose clinically aneurism of the thoracic and of the abdominal aorta. He seems to have seen many cases and to have been very familiar with the conditions.[2]

[1] It is not possible to frame a definition to include every condition which we now speak of as aneurism. For example, dilatation of the aorta, the uniform enlargement of arteries of the third and fourth dimension, and the abnormal communication between vessels are not within this definition.

[2] Roth's *Andreas Vesalius*, 1902, p. 239.

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Of the sixteenth century writers, Ambroise Paré gives by far the best account, and he recognized aneurism by anastomosis, rupture, erosion, and wound. He describes very well the character of the pulsating tumor, the noise or blowing sound associated with it, the frequency of thrombosis in the sac, the occasional calcification of the thrombi, and he first suggested the relation of aneurism with syphilis. For the next one hundred and fifty years there was a great deal of discussion about the mode of origin of aneurism, whether produced by dilatation of the coats or by their erosion and rupture, of which an excellent account is given by Friend.[1]

Lancisi, the distinguished Roman physician, wrote the first great monograph on the disease (*De Aneurismatibus*, Romæ, 1728), a superb work, with excellent illustrations. He recognized the influence of a bad habit of the body, particularly of syphilis, and even spoke of a "venereal aneurism." Trauma and the weakening of the coats of the vessel by disease were regarded as important causes. He divided aneurism into true and false, the one arising from weakening of the texture and the power of resistance of the arteries, and the other by traumatism, whether from external causes or from rupture due to increased force of the impulse of the blood. From this division by Lancisi dates a long struggle over the forms of aneurism, of which writers recognized a *true*, in which all the coats were dilated, a *spurious*, in which one of the coats was ruptured and the others dilated, and the *mixed*, in which the coats were dilated and subsequently, by rupture, a true was converted into a spurious aneurism. There is a very rich literature on the subject in the eighteenth century. Morgagni, in particular, made a most accurate study of aneurism, and his familiar work *De Sedibus*, etc., 1761, contains many interesting histories of cases with the postmortem appearances. He recognized, too, the great influence of syphilis. William Hunter (1757) made an important contribution on the subject of arterio-venous aneurism.

In 1804 appeared the famous work of Scarpa (a monograph in folio, translation by Wishart, Edinburgh, 1808), who insisted upon the important fact that internal aneurism also arises from rupture in consequence of degeneration or ulceration of the coats. He was the first to lay special stress upon the importance of the media in maintaining the strength of the vessel. Independently of Scarpa, the great French surgeon, Larrey, also insisted that bursting of the coats of the artery was the essential cause of aneurism.

Scarpa did not regard the dilated aorta as, in reality, aneurismal, holding that form only to be aneurism which arises "in some point of the parietes of the arteries from the rupture of their proper coats." Hodgson, in his well-known treatise,[2] believed that rupture of the internal and middle coats, either by trauma or following disease, was the chief cause of aneurism, but, in opposition to Scarpa, he also described as aneurism the permanent dilatation of the whole circumference of the vessel, due to loss of its natural elasticity. Allen Burns (1809) took very much the same view. Rokitansky, in his great monograph on diseases of the arteries (1852), regarded spontaneous aneurism as arising, first, through inflammation and suppuration of the arterial wall; secondly, through spontaneous tears of both the inner coats; and third, the common form which follows the disease of the coats

[1] *History of Physic*, fourth edition, vol. i, pp. 183 to 203.
[2] *Diseases of Arteries and Veins*, London, 1815.

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of the vessel, whether it results in a diffuse cylindrical dilatation or in the formation of a saccular tumor.

An important study by Helmstedter[1] from von Recklinghausen's laboratory showed that in the common spontaneous aneurism, splits and tears of the elastic coat of the media were the primary and important changes. The figures accompanying his paper show an aorta which we would now recognize as syphilitic, and microscopic pictures just such as have been described of late, as the mesaortitis due to this disease.

From this time on very special attention was paid to the condition of the middle coat, and in 1875, Köster brought forward the view that not an endarteritis but a mesaortitis of special form was the essential factor in aneurism. Two great studies appeared in Germany in the last quarter of the nineteenth century, one by Eppinger, as a supplementary Heft of vol. xxxiii of the *Arch. f. klin. Chirurgie*, 1887; the other by Thoma, in vols. cxi and cxii and cxiii of Virchow's *Archiv*. Eppinger regarded as the primary event the rupture of the media, particularly of the elastic elements, which led to the gradual saccular dilatation at one spot in the wall of the vessel. He did not regard the diffuse dilatation of the artery as a true aneurism. He also described most fully the erosion, verminose, and mycotic forms.

Thoma, too, regarded weakness of the media as the primary change, although he did not lay so much stress on rupture of the elastic elements, believing that a disturbance of nutrition and an atrophy of the media lessened its power of resistance. He brought his theory of aneurism into line with his well-known views on arteriosclerosis, believing that the thickened plaques of the intima were compensatory to the loss of substance in the media. He gives illustrations which show that this compensatory thickening may even be sufficient to obliterate the localized bulging of a small aneurism. He thought it was only in the rapid growth of the aneurism, in consequence of the yielding of the weakened media to the internal pressure, that prevented the compensatory endarteritis from keeping pace with it. His study of the dilatation—aneurism of the aorta—is by far the most important that has been made.

During the past few years the old views of Paré, Morgagni, and others on the influence of syphilis in cause of the disease have been amply confirmed. The careful study by Welch (1876) called attention to the subject, but the work of the pupils of von Recklinghausen and of Köster on the histological changes in the media, the studies of Heller and the improved methods of technique have given a great stimulus to this view. The studies of Benda and of Chiari[2] and the paper by Benda[3] give full summaries of the recent work on mesaortitis in its relation to syphilis and aneurism.

The important monographs for reference are Crisp (1846) and Broca (1856). The papers of Sibson (collected works) are also of great value.

Classification.—It is not easy to make a satisfactory division of the various forms of aneurism. The following will be found a useful one for practical purposes:

1. *True aneurism* (A. verum, A. spontaneum), in which one or more of the coats of the artery form the walls of the tumor.

[1] *Du Mode de Formation des Aneurismes Spontanes*, Strasburg, 1873.
[2] *Verhand. d. deutsch. path. Gesellsch.*, 1904.
[3] Lubarsch and Ostertag's *Ergebnisse*, 1904.

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(*a*) *Dilatation aneurism.*

1. Limited to a certain portion of a vessel—fusiform aneurism, cylindroid aneurism.
2. Extending over a whole artery and its branches—cirsoid aneurism.

(*b*) *Circumscribed saccular aneurism*—the common form in the aorta in which there is distention of two or more of the coats, or distention of the adventitia after destruction of the intima and media.

(*c*) *Dissecting aneurism*, with splitting of the coats to a greater or less extent and occasionally with the formation of a new tube lined with intimal endothelium.

2. *False aneurism*, following wound or rupture of an artery, causing a diffuse or circumscribed hæmatoma.

3. *Arterio-venous aneurism*—communication between artery and vein, either direct—aneurismal varix—or with the intervention of a sac—varicose aneurism.

4. *Special forms*, such as the traction aneurism, the erosion and parasitic forms, which have a pathological rather than a clinical interest.

Etiology and Pathology.—Incidence.—That the number of aneurisms differs in different localities has long been recognized. In Vienna, von Schroetter states that of 19,300 postmortems in ten years, there were only 230 aneurisms. Eppinger found only 22 in 3149 postmortems. At St. Bartholomew's Hospital, during thirty years, there were 631 patients with aneurism. At Guy's Hospital, between 1854 and 1900, there were 18,678 necropsies, with 325 cases of aneurism. There were 1078 deaths from aneurism in 1905 in England and Wales. The statement is usually made that it is more common in Great Britain and Ireland than on the Continent.

Age.—The large statistics of Crisp, 555 cases of aneurism in different situations, show the greatest frequency to be between the ages of thirty and forty years, 198 cases; between forty and fifty, 129. With this accords the statistics of Lebert and of Liddell, and it is of importance as showing that the incidence of the disease is below the age at which arteriosclerosis is met with. Of the 898 deaths from aneurism in males in England and Wales in 1905, 462 occurred between the thirty-fifth and fifty-fifth years. It may occur at any age. Jacobi and, more recently, Le Boutillier[1] have collected the statistics of aneurism in the young. The latter found in the literature 80 cases in persons under twenty years of age; only 14 were under twelve years of age, and the youngest was in a child of two. Eighteen of the cases were of the thoracic aorta, 5 of the abdominal. In the very young, congenital syphilis plays an important part, as in the remarkable case reported by Willson and Marcy in a child aged four years with extensive arterial disease and a large aneurism of the arch of the aorta. In the peripheral vessels the aneurisms are often of embolic origin. In extreme old age latent aneurism is not uncommon, either in the form of the dilatation of the arch or of small, saccular pouching of an atheromatous aorta.

Sex.—In Crisp's statistics the ratio of males to females was 5 to 1, and this is a fair average for aneurisms of all sorts. In 1905, 898 males and 188 females died of aneurism in England and Wales.

Occupation.—Hard workers, the strikers in foundries, the dock workers, soldiers, sailors, and the very muscular and robust men are chiefly affected,

[1] *American Journal of the Medical Sciences*, 1903, cxxv, p. 778.

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but the disease may occur in feeble individuals who have never worked hard with their muscles. For years it has been known that soldiers were peculiarly liable to the disease, and the studies of Myers, Welch, and others called attention to the great frequency of aneurism in the British army. This reputation is still maintained. The recent figures given for the British army (1905) home contingent, strength 118,224, show 18 deaths from aneurism. In Germany (1904 to 1905), with a strength of 555,777, there were 4 cases of aneurism; and in Italy (1903), with a strength of 206,468, there were 6 cases of aneurism. The high percentage in the British army is undoubtedly associated with the great prevalence of syphilis. For the year ending September, 1900, the incidence of syphilis in the German army was 18.5 pro mille; in the Austrian, 64 pro mille; and in the English, 122.4 pro mille. In the British navy the figures for five years, as sent by Sir Herbert Ellis, Director General, are as follows: 1902, force 99,600, cases 16; 1903, force 103,100, cases 23; 1904, force 110,570, cases 13; 1905, force 111.020, cases 22; 1906, force 108,190, cases 29. Bassett-Smith calls attention to the frequency of aneurism at the Naval Hospital, Haslar—47 cases in seven years.

Race.—The Anglo-Saxon is stated to be more subject to the disease. The statistics of Guy's Hospital and of the Vienna General Hospital quoted above show a decidedly greater proportion in London. In the United States of America aneurism is common among the working classes. It is more frequent among the negroes of the Southern States. In the wards for colored patients at the Johns Hopkins Hospital arterial disease and aneurism were relatively much more common than in the wards for the whites. The figures relating to aneurism are as follows: Of 345 admissions to the medical wards for aneurism, 213 were white and 132 colored (the proportion of total admissions of white to colored is about 5 to 1).

Determining Causes.—The determining causes of aneurism of the aorta are three: First, poisons which lead to changes in the coats of the vessel; second, conditions which increase and keep up the arterial tension; and third, internal trauma, the strain of muscular effort, particularly in the fourth decade, when the vital rubber begins to lose its elasticity.

Among the most potent poisons in causing arterial changes are those of the acute infections, and among these the first rank is taken by *syphilis*. Someone has well remarked that "Venus loves the arteries." It has already been mentioned that the older writers, particularly Paré, Lancisi, and Morgagni, knew of the close association of lues and aneurism. Among modern writers the connection was referred to incidentally, but it is only a little more than a quarter of a century since investigations have shown the remarkably high percentage of syphilis among subjects of the disease. In his well-known investigation,[1] Francis H. Welch, of the British army, found that 66 per cent. of his series had had syphilis. He described very clearly, too, the macroscopic changes in the aorta, particularly the cicatricial-like puckering of the intima. The constriction of the clothing and the temporary forced exercise he regarded as secondary elements. Subsequent figures have strengthened this belief: Malmsten, 80 per cent.; Hampeln, 82 per cent.; Heller, 85 per cent.; Etienne, 69 to 70 per cent.; Pansini, 65 per cent., or, including doubtful cases, 84 per cent. On the other hand, Hansemann

[1] *Medico-Chirurgical Society's Transactions*, 1876.

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found only 18.75 per cent., and he does not regard all cases of aneurism even in syphilitic subjects as due to syphilis. It is notorious that a history of infection, even in persons with well-marked signs of the disease, is not easy to get, particularly in women. There are a great many cases in which syphilis is latent, but the more closely the question is looked into the more one becomes impressed with the importance of lues as the essential factor in the causation of aneurism in persons under forty-five years of age.

The recent studies of Heller, Döhle, Chiari, and Benda have confirmed the views of Köster, that the primary change is in the media, and there is now very generally recognized a syphilitic aortitis with definite characteristics. Macroscopically, it may be limited in extent, localized at the root of the aorta, or about the orifice of an aneurism, or there is a band of an inch in width on some portion of the tube, while other parts of the aorta and its branches are normal. In other instances the intima is involved, not with the usual plaque-like areas of atheroma, but there are shallow depressions of a bluish tint and short transverse or longitudinal puckerings, sometimes with a stellate arrangement; or the intima is pitted and scarred with small depressions and linear sulci. Microscopically the most important changes are found in the media and adventitia: (*a*) perivascular infiltration of the vasa vasorum; (*b*) small-celled infiltration in areas of the media, with (*c*) splitting, separation, and destruction of elastic fibers and the muscle cells. The process is largely a productive mesaortitis, and so marked may be the foci in the adventitia and media that they look like miliary gummata, and, in fact, were so described as far back as 1877 by Laveran and by Heiberg. The intima over these areas may be perfectly normal, but it often shows signs of thickening with fatty degeneration and the production of hyaline. Similar changes have been described in the larger bloodvessels in cases of congenital syphilis by Weissner, Bruhns, and Klotz. And lastly, the specific nature of this mesaortitis has been determined by the detection of the spirochæte by Schmol and others.

The experimental production of aneurism bears out this view. The high pressure caused by injection of adrenalin produces a fracture and separation of the elastic fibers of the media, and over these areas where the wall is weakened the intima may split with the formation of a localized aneurism, sacculated or dissecting, or the intima may gradually yield without actual rupture.

The following are among the important features of syphilitic aneurism: It occurs, as a rule, in persons under forty; the ascending arch is most apt to be involved; angina pectoris may be an early symptom; aortic insufficiency is often associated with it; the aneurisms are frequently multiple, five, seven, and nine have been described; the small cup-formed sacs, of which there may be four or five in the ascending arch, are almost always syphilitic; other luetic features may be present, gummata of the liver or bones; there are signs of locomotor ataxia or the husband may have tabes and the wife aneurism, or, as in a case reported by Jaccoud, both husband and wife have aneurism; and lastly, antisyphilitic remedies may relieve the symptoms.

Other acute infections play a less important role. There are two ways in which aneurism may be associated with the specific fevers. In any one of them local spots of degeneration, usually of the intima, may occur, or patches of mesaortitis may develop, leading to a weakening of the wall.

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Thayer and others have shown the frequency of these changes after *typhoid fever*, and the same may happen after *influenza*, *pneumonia*, *erysipelas*, and *scarlet fever;* there is doubt about *malaria*, upon which some of the French writers lay stress. The other way is associated with the endocarditis of the specific fevers. Direct extension to the aorta from vegetations on the valves may take place, but more frequently the process is embolic, with patches of mesaortitis over which the intima ruptures, just as occurs in the experimental production of aneurism. In the aortitis of *rheumatic fever* one or other of these forms may be followed by aneurism; but many of the cases described as aneurism of the aorta in this disease are instances of the dynamic dilatation associated with aortic insufficiency and a huge left ventricle. But true aneurism does occur. In a case recently reported by Renon, the patient, aged sixteen years, developed signs of aneurism very rapidly with aortic insufficiency in the course of rheumatic fever. Death occurred from hemorrhage. The difficulty in the diagnosis of these cases will be referred to later. The type arising in the acute infections will be considered in a special section on mycotic and embolic aneurisms.

Tuberculosis is frequently met with as a complication of aneurism, 25 to 29 per cent. (Soltau Fenwick), but it plays a very minor part in the etiology, except of the erosion form occurring in tuberculous cavities in the lungs. The aorta or one of its main branches may be eroded from without by a tuberculous gland with the formation of an aneurism.

Intoxications.—Alcohol favors arterial degeneration perhaps directly, but more often indirectly, as one of the causes of permanent high tension. It is one of the three factors which makes aneurism common among the laboring classes, although it plays a minor role in comparison with syphilis and hard work. There are some statistics, those of Etienne for example, which give a very low percentage of history of alcoholism—only 28 among 240 cases. *Tobacco* which has been shown experimentally to have an important influence in causing arterial degeneration, cannot be said to play any part in the etiology of aneurism. *Lead* has, in man, a decided action in causing degeneration of the arteries and in this way predisposes to aneurism.

All conditions which favor an excess or a retention in the system of the waste products of nutrition lead to arterial degeneration, and in a few cases to aneurism, but the causes of arteriosclerosis and of aneurism are by no means identical.

Embolism as a Cause of Aneurism.—In 1888 a man died in the Montreal General Hospital with fever and signs of aortic insufficiency and aneurism. The postmortem revealed an extraordinary condition—acute endocarditis of the aortic segments, with five aneurisms in the arch of the aorta. The largest of them, the size of a billiard ball, projecting to the right just above the aortic ring, was very thin walled and had numerous greenish vegetations on its lining wall, which at one point had perforated into the pericardium. The intima of the aorta was smooth, and on the arch above the larger aneurism were three small ones not larger than cherries. From the side of the intima they were not visible, but their site was indicated by the pressure of small, fungoid outgrowths. These were seen on the edges of narrowed slits of the intima which led directly into the small, saccular aneurism. This was the first instance in which the mycotic character of this type of aneurism was recognized. It has since been studied very carefully by numerous observers.

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There are two modes of formation: (*a*) In the smaller vessels the condition, as described by Ponfick and by Pel, is due to the direct lodgement of emboli with infection and erosion of the wall and the production of an aneurism. A number may occur in different vessels. Libman reports a case with four aneurisms on the mesenteric vessels, a fifth on the right branch of the hepatic artery, a large one on the right femoral, and before death, right hemiglegia with aphasia probably from rupture of a mycotic aneurism of the left sylvian artery. In another case of Libman's, with mitral and aortic endocarditis, a mycotic aneurism of the left femoral artery perforated the vein with the formation of an arterio-venous aneurism. In this form there is no question of the direct local infection of the intima by the emboli.

(*b*) In the case of the multiple mycotic aneurisms of the aorta, it is a different matter. Here, in all probability, the emboli pass to the vasa vasorum and cause a mesaortitis with weakening of the wall. The intima splits, and in this way a small aneurism is formed. In the case reported by the writer, and in other instances, particularly the one reported by John McCrae,[1] splits in the aorta were sharp and defined as if made with a knife. There may be no disease of the intima itself in the neighborhood. With this view Eppinger concurs, and he remarks that the multiplicity of the lesions within a small radius is evidence of the embolic nature. In other instances there is a verrucose aortitis which has extended directly from the valves and is not of an embolic nature; and in a few rare instances this occurs in rheumatic fever. Embolic aneurisms are not always mycotic. A fragment from a calcified vegetation dislodged into the circulation may lacerate the intima at the point of lodgement with the formation of a traumatic aneurism. The writer saw a remarkable case of this kind in the Radcliffe Infirmary with Dr. Mallam: A man with aortic insufficiency and a remarkable musical diastolic murmur, had been under observation for a long time, and had frequently been used for examination purposes. Suddenly one day he had an agonizing pain in the calf of one leg, which became swollen, hot, and painful. As the swelling subsided a pulsation was noticed, and he recovered in a few weeks with a well-marked aneurism of the posterior tibial artery. The musical quality of the diastolic murmur disappeared entirely. No doubt a small calcified spike at the edge of one valve had been dislodged. A large majority of the cases occur in connection with ulcerative endocarditis. Pain of an agonizing character is present in the area where the emboli lodges. Peri-arteritis, swelling, and infiltration of the surrounding tissues usually occur, and it may not be until their subsidence that the pulsation is noticed.

Relation of Aneurism to Atheroma.—Everyone who has made many postmortems, particularly in very old people, must have been struck with the fact that the extent of atheroma bears no relation whatever to the frequency of aneurism. The aorta may be a calcified tube, with an intima as rough as the skin of a crocodile, without the presence of aneurism. The truth is the *endarteritis deformans* of Virchow is not necessarily associated with weakness of the media and adventitia. Chiari made a careful comparison between a series of cases of ordinary atheroma of the aorta and of mesaortitis. Of his conclusion, which has special importance in the differentiation of these two groups, a summary may be quoted: "In atheroma he found a primary

[1] *Journal of Pathology and Bacteriology*, 1905, vol. x, p. 373.

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change in the intima, a thickening with a tendency to hyaline, mucoid, or fatty degenerations, leading to necrosis or calcification. In the early stages the media and adventitia appeared normal. In the later stages changes similar to those in the intima appeared in the inner layers of the media, while the outer layers showed proliferation of the vasa vasorum with small-celled infiltration around them, and in the adventitia there was in some cases considerable infiltration around the vasa vasorum, the walls of which showed some degree of proliferating endarteritis. These inflammatory changes, however, remained localized, and even in advanced cases did not reach a very great degree of intensity. Only by the actual pressure of a large calcareous patch was the media destroyed to any great extent. He considered that such a condition could be produced by any injury to the vessel, infections or intoxications, or the disturbance of nutrition which accompanies old age" (abstract by C. N. Aitchison, M.B.). In other groups the change was a mesaortitis in syphilitics or the subjects of general paralysis and the intima presented the furrows and scars already described.

High Blood Pressure.—Next to destruction of the elastic fibers of the media by a mesaortitis this is the most important single factor in the causation of aneurism. It acts in two ways: if permanent it leads to arteriosclerosis and weakening of the media, so that there is dilatation, either diffuse of the aortic arch or in spots. More important still is the sudden increase of tension following a rapid movement or severe strain, as in lifting, jumping, or the straining movements at stool or in the act of parturition. Here the danger is that by an internal trauma over the weakened media the intima may tear with the formation of a small sac. The process may be traced in the production of *experimental aneurism.* With adrenalin, tobacco, and bacterial poisons, extensive degeneration of the aorta and larger vessels is caused, but what is most interesting in this connection is the formation of aneurisms, either (1) multiple bulgings in areas in which the media is greatly weakened, causing pouch-like aneurisms, just such as we see in the endarteritis deformans of old people; or (2) the normal-looking intima is split over an area of mesaortitis, a clean-cut, knife-like incision, beyond which is a little saccular dilatation or the beginning of a dissecting aneurism. I am indebted to Klotz, in Adami's laboratory, and Rickett, of Cambridge, for showing me their specimens which illustrate this mode of formation of aneurism. Fischer[1] figures very well these splits of the intima, over local areas of degeneration, identical with those met with in the human aorta.

External trauma has a definite influence on the causation of aneurism. Vesalius notes this in one of his cases. Many instances have followed blows on the chest, falls, or the jar of any accident. While rupture of the healthy aorta may occur in these cases it is more probable that the intima ruptures over a patch of mesaortitis, and in this way the aneurism starts. Stern[2] has collected a large number of cases from the literature. The aneurism may appear in a few days or not until many months have passed.

In a few rare cases aneurism of the aorta is of the *erosion* type. A tuberculous focus may involve the wall of the aorta, as in a case reported by Councilman. A bullet lodged in the wall without perforating it has been followed by aneurismal dilatation (Freyham).

[1] *Deutsch. med. Wochenschrift*, 1905.
[2] *Ueber traumatische Entstehung Inneren krankheiten*, 1896.

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Other causes may be mentioned. Mickle has called attention to the frequency of aneurism in the *insane*. This and the not very uncommon co-existence with *locomotor ataxia* is probably a parasyphilitic association. Lee Dickenson has described aneurism in connection with *hypoplasia of the aorta*. Both of his cases were in young adults with thin, narrow aortas, free from disease; one presented three aneurisms.

Number, Form, and Size of Aneurism and Vessels Affected.—*Number.*—In the aorta the aneurism is usually single, but three, four, five, even a score or more, may be present. The multiple cup-shaped tumors in young men are always syphilitic. The mycotic aneurisms are often multiple; in one of the writer's cases there were five in the arch of the aorta. In the embolic form there may be a dozen or more in the smaller vessels. In certain individuals aneurism may occur in different vessels, simultaneously or in succession.

The late Thomas King Chambers, whose clinical lectures "On the Renewal of Life" are still well worth reading, had first an aneurism of the left popliteal artery, then of the right, and finally of both carotids.

Form.—In the aorta there are two great types, the *cylindrical*, or *fusiform*, and the *sacculated*. In his study[1] Thoma calls attention to the physiological bulgings of the aorta: "The ascending aorta in the region of the semilunar valves presents an onion-shaped dilatation, the bulbus aortæ, in which are the sinuses of Valsalva. Immediately above the valves the lumen narrows distinctly, becomes circular, and then undergoes a second dilatation directed forward and to the right, known as the sinus quartus sive maximus Valsalvæ. This unilateral, spindle-shaped dilatation of the aorta also disappears again before the vessels of the neck are given off. After the origin of the left subclavian there follows a narrower portion of the lumen, the isthmus aortæ, after which the vessel again widens." As given in the plates illustrating the article, Thoma shows that in pathological states of the arch these physiological bulgings are followed; one or other or all of them may show dilatation, or the whole arch may be involved, forming a definite spindle. In other instances the arch is a huge, flabby sac scarcely retaining a semblance of its shape. Typical spindles are seen too in the arteries of the second and third dimensions, rarely in the smaller vessels. The cylindrical and fusiform are usually combined, as the dilatation tapers at either end. Sometimes the whole aorta or a large section of it is represented by an enlarged cylinder.

The *sacculated* form, in which there is a definite protrusion of one side of the wall, is the more common. The shape of the sac will depend on the extent of the area of the primary weakness of the wall; if large, the sac will be diffuse and crater-like; if small in relation to the aorta, it may have a small orifice, slit-like, oval, or round, leading into a circular pouch. Some sacs are flat, saucer-shaped, others cup-shaped, others pear-shaped, almost pedunculated, with a narrow neck. The saccular aneurism may arise on the wall of a diffuse dilatation, or a saucer-shaped sac may have two or three small ones upon it. Occasionally there is seen an aneurism of multilocular aspect, which has arisen from the excessive development of these secondary sacs.

In the small arteries, as of the brain and kidneys, these same types are

[1] Untersuchungen über Aneurismen, *Virchow's Archiv*, cxi.

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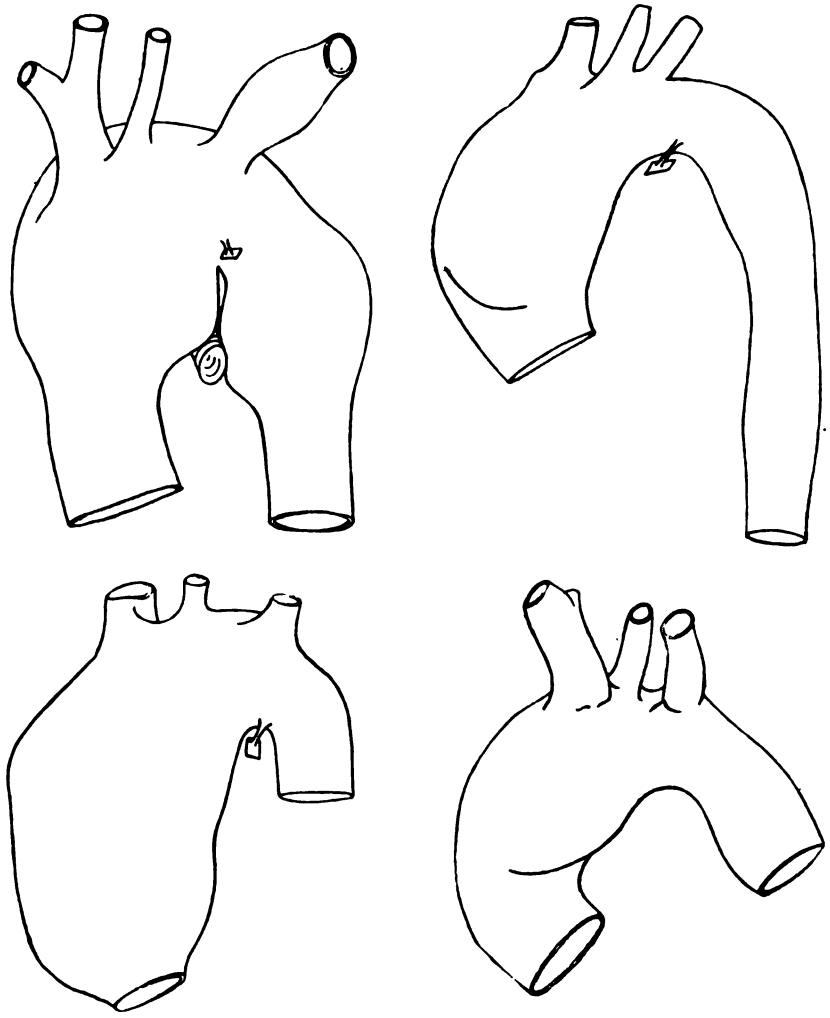
seen—the saccular more often than the fusiform. The special forms of dissecting and arterio-venous aneurisms will be described later.

Size.—From a pin's head to the head of a child. There are almost microscopic tumors of the small arteries, while a sac connected with the

FIG. 44



Forms of dilatation in aneurism of the arch of the aorta. (After Thoma.)

aorta may fill one-half of the chest. When perforation of the chest wall occurs, or when there is a diffuse aneurism of the abdominal aorta, the size of an adult head may be reached, and with its contents the aneurism may weigh five or six pounds.

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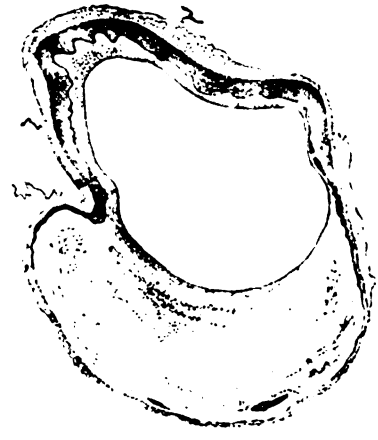
Vessels Affected.—On this point Crisp's statistics are still the best available:

Pulmonary artery	2
Thoracic aorta	125
Abdominal aorta	59
Common iliac	2
External iliac	9
Gluteal iliac	2
Femoral iliac	66
Popliteal	137
Posterior tibial	2
Innominate	20
Carotids	25
Intracranial	7
Temporal	1
Ophthalmic	1
Subclavian	23
Axillary	18
Suprascapular	1
Brachial	1
Total	501

Life History of an Aneurism.—Against the incessant strain offered by the pumping of blood sixty to eighty times a minute, the artery is protected by the elastic and fibrous tissues of the media and adventitia. Weakened at one spot and yielding, it is then a struggle between the blood pressure and the remnants of the tube at the affected spot—an unequal struggle, as the sac gradually yields. But nature does not rest passive in the matter. Only in the very acute cases is no attempt seen to limit the mechanical progress of the disease. In nearly all aneurisms healing of the breach is attempted by two processes, with two tissues, the one mural and the other hæmic, a new-growth of connective tissue and fibrin formation.

FIG. 45



Cross-section of the ophthalmic artery showing diffuse arteriosclerosis and healing of an aneurism by intimal thickening. (After Thoma.)

(*a*) Connective-tissue healing of an aneurism, seen to perfection only in small forms, is an intimal affair; in large sacs the adventitia play the chief part. We owe to Thoma the first good account of this method of healing. Fig. 45, here reproduced, shows a small sac on a branch of the ophthalmic artery entirely obliterated, with a growth from the intima in such a way that the inner surface of the artery and of the sac are on a level. Although the same process may go on in the larger vessels (and Thoma figures an example in the abdominal aorta), it is much less rare than in the small branches. In every aneurism still lined with intima this compensatory thickening is to be found. But under the influence of the blood pressure the sac, as a rule, grows at such a rate that the endarteritis cannot keep pace with it. In the

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common saccular aneurism the reparative process from the adventitia is much more important. There is active proliferation of the fibrous elements, and although it may yield and be thin at the point of greatest pressure, in the larger sacs there is found great thickening which is not always easy to differentiate from the surrounding connective tissue.

The lining of an aneurism may be the thickened intima (which is only the case in very small tumors), the media, in whole or in part, or, as the sac enlarges, the adventitia alone. Then comes a stage in the growth of the larger tumors in which part of the sac is no longer composed of an arterial coat, but is in direct connection with adjacent tissue, bone, lung, skin, or the structures of the mediastinum. In the big dilatation aneurism the intima may be everywhere unbroken, but thickened and roughened with calcareous plates and areas of atheromatous softening. In the saccular form the intima may be traced only to the orifice or for a short distance into the wall of the sac.

The second great element in the repair of an aneurism is thrombosis, the deposit of laminated fibrin in the sac. We are as yet ignorant of the precise conditions under which this process takes place. It does not occur in every case, even under conditions which look the most favorable. In a typical degree the deposition of fibrin in seen in the sacs with narrow necks, but it may be seen in the fusiform dilatation of any part of the aorta. In cutting across an aneurism in which this process has been going on, firm, hard, leathery sheetings of grayish-brown fibrin are seen, arranged in layers which may be peeled off like the flakes of an onion. In large sacs from 25 to 50 laminæ may be counted. The gradual formation of these is most interesting. One often finds on the lining membrane of a small-sized sac most remarkable deposits of platelets, usually ribbed like sand on the seashore or arranged in a tracery or network. The areas with the platelets show as grayish-white, soft thrombi, quite different in appearance to the reddish-brown ground substance on which they are deposited. The lamination may be in some way due to a successive deposition of platelets with which, as we know, the thrombogen is associated. Gradually the aneurism may become filled even to the mouth, and in this way permanent healing may be effected. At first the layers of fibrin are reddish brown in color, but in the very old sacs they are grayish white, and occasionally lime salts are deposited, so that the whole becomes a firm, calcareous mass.

Effects of Compression.—With the gradual growth of the sac remarkable effects of compression are seen. Passing anteriorly, an aneurism of the arch erodes the sternum, destroys the costal cartilages, fractures the ribs, which gradually become absorbed, and finally, there may be a hole in the front of the chest into which the two fists may be placed. Posteriorly, an aneurism of the descending thoracic aorta may perforate the chest wall and destroy four or five ribs, causing complete atrophy of the muscles in its course, and appear beneath the skin as a large flabby sac, as is very well shown in Fig. 50. Not less remarkable effects of erosion are seen in the spine, the bodies of three, four, or five of which may in large part be absorbed and the roughened bone forms part of the wall of the aneurism. A remarkable fact, noted by Morgagni, is that the intervertebral disks are not destroyed at the same rate as the bone, and may remain more or less intact while the bodies are deeply eroded. The exact method of this destruction of bone is much discussed. Some have ascribed it to a dis-

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solving action of the blood, others believe it to be entirely mechanical, due to the pressure and shock of the systole. Cornil and Ranvier describe it as a rarefying osteitis, a low grade of inflammation by which the bone is gradually removed. Other effects of compression and the modes of perforation will be described later.

ANEURISM OF THE HEART.

1. **Aneurism of the Valves.**—Weakness of the tissue of the valve results from erosion, from myotic ulceration, or from softening of an atheromatous focus. There are acute and chronic forms. The acute valvular aneurism is seen most commonly on one of the aortic segments projecting from the ventricular side in globular form of the size of a pea or of a small nut. Sometimes it involves the entire valve. It may be at the line of attachment, so that there is partial aneurism of the sinus of Valsalva as well. It may be the only lesion, although more frequently it is associated with destructive changes. In very many instances the aneurism is perforated. Two, three, or even four little sacs have been found. Involvement of the mitral segments is not so common—the anterior valve more frequently than the posterior. The chronic atheromatous aneurism is a very different affair. Following the softening of a subintimal focus, it is usually seen in sclerotic or partially calcified valves, and in the aortic more often than in the mitral segments. Thrombi may be deposited; in one instance they were firm and laminated.

2. **Mural Aneurism.**—Two forms may be recognized, the acute and the chronic.

Acute Aneurism.—Acute aneurism, an event in connection with ulcerative endocarditis of the heart wall, is seen most frequently on the left side in the upper portion of the septum near the aortic ring, but it may occur on the right ventricle, and even in the auricles. Perforation is apt to take place into the pericardium or one of the other cavities, or into one of the larger vessels. An interesting variety of this is the dissecting aneurism of the heart, of which Vestberg[1] has collected 60 cases.

Chronic Aneurism.—This is an event in connection with fibrous myocarditis. It is not very uncommon, particularly the slighter forms. Strauch collected 55 cases which occurred in Berlin, chiefly at the Charité Hospital within ten years. There were 3 cases at the Johns Hopkins Hospital among 3000 postmortems. It is much more common in men than in women—64 out of 80 cases (Wickham Legg); 38 out of 55 cases (Strauch). The majority of the patients are above fifty years of age. A case has been reported in a boy of ten (Rosenstein).

Etiology.—The etiological factors are those of arteriosclerosis and chronic myocarditis. In Strauch's series 44 of the cases presented myocarditis alone without valve lesion. It is usually stated, and it certainly has been the writer's experience, that the coronary arteries are involved or the anterior branch is calcified and narrowed; but Strauch's cases, which seem to have been very carefully studied, do not bear out this view, as only 15 showed involvement of the coronary arteries. He regards it as

[1] *Nordiskt Med. Arkiv*, 1897.

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a special pathological change, a degeneration which is difficult to connect with any other heart lesion. Syphilis did not appear to be a factor in many cases. The left ventricle is affected in almost every instance, in all of Strauch's series, and in a large majority the apex region is involved, extending toward the septum. Usually single, there have been cases reported with two or even three aneurisms. In the most characteristic form there is a globular distention of the apex region of the heart, with perhaps slight thickening of the pericardium or a definite change in the appearance of the muscle. The tumor may be the size of the fist, or even larger. From within thrombi are usually seen, attached to a sclerotic endocardium. On section of the wall of the sac the heart muscle may in great part be converted into fibrous tissue. The thrombi have been found calcified. As a rule, the sac is flat, in a few cases quite globular and communicating with the cavity of the ventricle by a narrow orifice. Cases have been described in which the sac has been larger than the heart itself.

Symptoms.—The symptoms are very obscure, and it is rarely possible to make a diagnosis. The cases are usually mistaken for chronic myocarditis, or the diagnosis is made of the associated valvular lesion. As the aneurism is at the apex and enlarges the left ventricle, the features of hypertrophy and dilatation are usually present. Symptoms of angina pectoris are not infrequent. Strauch has carefully analyzed the physical signs presented in a select group of his cases without throwing any very special light on the possibility of diagnosis.

DILATATION ANEURISMS.

There are two important groups: (1) In one, seen chiefly in the aorta and larger branches, the artery has passively dilated, owing to disease of its walls; (2) in the other, seen most frequently in small branches, there is an active dilatation due to growth and enlargement of the vessel.

Dilatation Aneurism of the Aorta.—New interest has been attached to this form since the introduction of the *x*-rays in clinical diagnosis. Formerly it was overlooked to a great extent even in the best clinics. In witness of this may be mentioned the striking fact that of the long series of cases studied by Thoma[1] scarcely one had been recognized in the wards, though under the care of one of the most skilful clinicians in Europe.

Joseph Hodgson,[2] in 1815, described what he called "a preternatural, permanent enlargement of the cavity of an artery," and distinguished it clearly from ordinary aneurism. He recognized its association with disease of the coats of the vessel, and remarked that saccular aneurism could be engrafted upon it. The dilatation, which might be partial or complete, affected most frequently the ascending aorta. He very acutely observes that the symptoms suggest organic disease of the heart rather than aneurism. Since Hodgson's date this form has been well recognized anatomically, but it has not received enough consideration clinically, and yet it is one of the most common forms in the aorta. Scarpa, too, in his great treatise, while recognizing dilatation of the whole tube of the aorta, regarded it as essentially

[1] *Virchow's Archiv*, cxi.
[2] *A Treatise on the Diseases of Arteries and Veins*, London, 1815.

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different from aneurism, although he says the two may be sometimes found together. Morgagni, who has overlooked so little in the morbid anatomy of aneurism, makes a clear division between two kinds, one in which the tumor occupies the whole circumference of the arterial tube, the other in which the aneurism only affects one side of the artery. Primarily a disease of the media causing weakening, there are usually associated changes in the adventitia and extensive alterations in the intima. Among the forms recognized by Thoma are: (1) the multiple spindle-shaped aneurism; (2) the single fusiform aneurism; (3) the saccular engrafted or spindle form; and (4) the tent-shaped or sphenoid, a special form in connection with the upper part of the thoracic aorta, which, he thinks, results from abnormal tension at this point just where the upper intercostal arteries are given off. He lays great stress on the involvement of the adventitia, and with the periarteritis he would associate the attacks of pain so common in this condition. While, as a rule, this form is met with in old persons and is associated with extensive endarteritis deformans, one meets with a few cases in which the arch is considerably dilated with a smooth or not much involved intima.

Associated quite frequently with this dilatation of the arch is insufficiency of the aortic valves, due either to a sclerosis and shortening of the segments or to dilatation of the ring itself. It is to this combination particularly that the French give the name, *Maladie de Hodgson*, but in the original description of this author it does not seem that he refers to the associated disease of the valve.

In young men with syphilis the process may be limited to the arch, which in any case is most common, but it may involve the entire aorta. In nearly all cases there is extensive endarteritis deformans with calcified laminæ and atheromatous erosions. The dilatations may be onion-shaped or spindle-formed. They may be multiple. Sometimes on the wall of the spindle-formed dilatation there are small saccular aneurisms. Thoma's admirable paper gives outline figures of the various forms, all of which owe their origin directly to the action of blood pressure on the diseased vessel wall.

The dilatation aneurism is very common, particularly in old people, and is often found accidentally. Only when of a very large size does thrombus formation take place in it. There is a remarkable specimen in the McGill Museum presented by R. L. Macdonell, in which the descending thoracic and abdominal aorta, and the iliacs were greatly dilated. The abdominal aorta forms a fusiform aneurism, which is filled with a densely laminated thrombus. In other instances the whole aorta is dilated, or the arch may be double or treble the normal size and without thrombi on the roughened intima.

Symptoms.—There are three groups of cases: (*a*) Latent: The condition is met with accidentally in medicolegal work or in the postmortem-rooms of almshouses and infirmaries, particularly among old people. The dilatation may reach an extreme grade without any special symptoms. (*b*) With the picture of *angina pectoris:* In the syphilitic aortitis in men under forty years there may be no dilatation of the arch, but in the senile dilatation of the arch angina is a common, sometimes the only, symptom. The attacks of pain may recur at intervals for several years without any sign of cardiac insufficiency. (*c*) In a third group the features are those of organic disease of the heart, usually of aortic insufficiency, characterized by attacks of vertigo, dyspnœa, cough, and the usual symptoms of cardiac failure, which may be

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present for weeks or months before the end comes. Hodgson recognized the fact that the clinical features of the condition were very often those of valvular disease. The incompetency of the valves may be due to the distention of the aortic ring.

Physical Signs.—*Inspection* may show a diffuse impulse over the manubrium, but in old persons with rigid chest walls and a calcified aorta there may be an extreme degree of dilatation without a visible impulse. The top of the aorta may reach to the sternal notch, and the innominate artery is elevated; but it is to be remembered that the throbbing in this situation is much more frequently due to the right carotid as it leaves the innominate, or to the innominate itself, than to the arch. The right subclavian is often visible above the clavicle, and Barié regards this as one of the best signs of dilated arch. An impulse may be seen on either side of the sternum in the second and third interspaces. Palpation may detect a systolic thrill, rough and harsh in cases of calcification of the intima, sometimes diastolic when the valves are insufficient. With one hand on the manubrium, the other on the spine, pressure may detect a deep pulsation. In the sternal notch the forcible throbbing of the dilated aorta may be felt. Tracheal tugging may be present. *Percussion* carefully made gives a dulness over the manubrium, varying in degree with the extent of the dilatation.

Auscultation.—A systolic murmur is heard, often of great intensity, and propagated into the vessels of the neck. There is nothing distinctive in it, nor does it differ from the bruit so often heard over the aorta in old persons with sclerosis. A diastolic murmur, if present, is more important, as it may be heard up the sternum, often quite loudly, and is even propagated into the vessels of the neck. The aortic second sound may be of a remarkably metallic quality and loudly heard up the sternum. O. K. Williamson has called attention to the high blood pressure in these cases, while in the ordinary saccular aneurism it is, as a rule, normal. Lastly and most important of all, the fluoroscope shows a pulsating shadow, larger and higher in position than the normal aorta, and which does not disappear in diastole.

Active Dilatation Aneurism. Cirsoid Aneurism.—No structures retain their powers of growth in greater degree than the arteries. Many physiological conditions demand the retention of this property; for example, the arteries of the uterus at term are four or five times as large as in the unimpregnated state. In tumors, in the enlarged spleen, in the proximal branches after ligation of a main trunk, the arteries not only increase in size, but there is an active development showing to what an extraordinary degree these structures possess the capacity for new-growth. With this power it is not surprising that we meet with instances in which spontaneously, at any rate from unknown causes, arteries enlarge. The condition is known as aneurism by anastomosis, racemose aneurism, or, more commonly, *cirsoid aneurism*. The arteries of the fourth and fifth dimensions are the most frequently involved, vessels, for example, of the size of the radial and its immediate branches, or of the temporal arteries. The dilatation may be confined almost entirely to the arteries themselves. In other instances the veins are involved, and the smaller vessels, even the capillaries, may be implicated, so that the structures form a diffuse angioma. The situations most frequently involved are the head and the hands, but the arteries of any part of the body may be affected and the aneurisms may be single or multiple.

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There are three important exciting causes. The dilatation may arise in small birthmarks or little angiomas, particularly those about the ear and forehead. With a gradual increase in size, the arteries become convoluted and throb forcibly. In a second group of cases the aneurism follows directly upon an injury, in one instance a burn on the hand, another, a blow on the head with a club, and the third, a slap on the face. And thirdly, in an interesting series of cases the tumor arises as a sequence or during an attack of fever. Two such cases are reported by Bazy.[1] In one, a man aged nineteen years, who had had an induration on the palmar surface of one hand during convalescence from an attack of typhoid fever, a dilatation of the vessels of this hand began, and in two or three years the radial was as big as the brachial. Reverdin reports a case of a man, aged thirty-one years, who ten years before had had an attack resembling typhoid fever. The exact nature was never very clear. Following it in a few weeks he noticed a little tumor over the left eyelid in which the color of the skin had changed. This gradually increased, and when seen by Reverdin just ten years later there was a pulsating tumor of the temporal region above the left eyebrow. At the Johns Hopkins Hospital, in 1903, we had a patient in whom multiple cirsoid aneurisms were present; following an attack of typhoid fever there was a decided increase in the size of the vessels. Reverdin suggests that all sorts of infectious arteritis may be the starting point of the aneurismal dilatation.

Symptoms.—Small tumors may cause no inconvenience. There may be slight swelling of the skin over the bunch of dilated arteries, and when the hand is placed upon it the individual vessels are felt to be convoluted and dilated; the pulsation is forcible, there is usually a thrill to be felt, and with a stethoscope a loud whirring murmur is heard. If the arteries alone are dilated, this may be systolic and single. In other cases where there are large venous anastomoses, the murmur is more or less continuous with systolic intensification. In other cases, particularly about the ears and temporal region, the skin itself is involved. There is marked swelling with a bluish tint, the dilated arteries are visible, telangiectases are present in the skin, or, if the whole process has started from a small birthmark or a nævus, the entire tumor may present the character of an angioma. The side of the face and head may be involved, and exophthalmos be present on the affected side. Huge tumors of this kind are reported, and they have at times increased with the rapidity of a new-growth. Arising spontaneously, they have been known to disappear in the same way. A remarkable case is reported by Fernell.[2] A man aged twenty years, had a large pulsating tumor above the right clavicle which had lasted many years and which involved all the branches of the thyroid axis except the inferior thyroid; the transversalis coli and suprascapular could easily be made out, greatly enlarged and tortuous. During an attack of measles, in which the temperature rose to 106.5°, the tumor looked very red and angry, and pulsated very strongly, as if about to rupture. A compress was applied and veratrum viride, ergot, and iron were given. Following the attack of measles the tumor began to subside, gradually the pulsation and thrill disappeared, and it shrank to a mass of hard connective tissue which could be rolled about.

[1] *Gaz. des Hôpitaux*, 1889, p. 1363.
[2] *St. Louis Courier of Medicine*, 1887.

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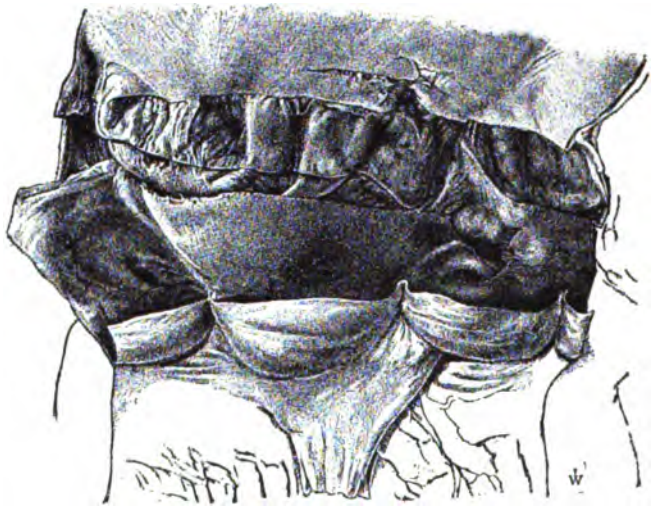
DISSECTING ANEURISM.

Splits and Fissures of Intima. Rupture of Aorta. Healed Dissecting Aneurism.—1. **Splits and Fissures of the Intima with Healing.**—In the artificial production of aneurism, already referred to, there is sometimes found over a patch of mesarteritis a small slit or fissure of the intima, cleanly cut as if with a knife, evidently due to rupture. Behind this there may be a small pouch-like distention of the media and adventitia, or a little dissecting aneurism. Precisely the same thing happens in man, and there may be spontaneous rupture of the intima in the form of a small slit one-fourth to one-half inch in length, or the entire circumference of the intima of the aorta may be cut through as if with a knife. A most remarkable circumstance is that these lesions may heal completely, leaving scars of the most extraor-

FIG. 46



Illustrating a complete transverse split of the intima of the aorta. (After v. Schrötter.)

dinary character. Deland has reported such a case.[1] Three years before the final attack the patient had had a severe attack of pain in the chest and unconsciousness, from which he had gradually recovered. Death occurred very suddenly from a fresh tear of the aorta and rupture into the pericardium. The cases are not very numerous in the literature. Von Recklinghausen describes the case of a woman who died postpartum of a rupture two inches long of the inner coat of the ascending aorta. In the descending aorta an inch below the duct there was a split of the intima completely encircling the tube which was entirely healed. Zahn reports a case of a woman, aged thirty-seven years, dead of pneumonia and an aneurism of the aorta. Sixty millimeters from the ring there were healed splits in the intima and the media.

[1] *Transactions of the American Climatological Association*, vol. xiv.

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The latter coat was not quite cut through, and this he thinks was the cause why a descending aneurism was not formed. Von Schrötter gives a figure[1] which is almost identical with the aorta in Deland's case.

By far the most important study in the healing of those splits and tears is in the well-known paper by Rokitansky.[2] He had not at that time seen a case of complete healing of a dissecting aortic aneurism, but he well remarks that the healing of the tears of the inner coat of the aorta, which he had figured, are not less remarkable. A man, aged sixty years, had been for eight weeks laid up with trouble in his chest and had become dropsical. When admitted to the hospital he was dyspnœic, had profuse sweats, with pain in the left thorax, and a feeble, irregular heart. Death took place on the second day. Above the aortic valve there were splits with separation of the internal coat. The edges of the splits were smooth, and where the middle coat was exposed it had also a smooth and fibrous appearance. Spontaneous healing had taken place. He reports five cases of these healed splits of the intima. In Deland's case, the heart of which was dissected by the writer, in the first attack the intima of the aorta had split in the entire circumference and there was a fibrous cicatricial ring just above the valves. There was no pouching, and the margins of the intima were rounded and smooth. It looked an old and healed lesion. Farther up the arch was the fresh knife-like split of the intima and a rupture into the pericardium.

2. **Spontaneous Rupture of the Aorta.**—Traumatic rupture is not uncommon in medico-legal work. Spontaneous rupture is rare, but it may occur in a vessel apparently healthy, either as a result of sudden strain or sometimes without any effort. It may occur during confinement or in sudden muscular effort. It has occurred in a healthy boy aged thirteen following prolonged exertion. In the majority of the cases it is an intrapericardial rupture. The intima may be smooth and the lesion is usually sharp and well defined, as if cut with a knife. The rupture in the external coat is rarely directly opposite that in the intima, so that there is usually some evidence of dissecting aneurism. The cases present very characteristic clinical features, the symptoms occurring in two stages.

The case reported by Linn[3] is a good illustration: a woman, aged twenty-nine years (who had twice miscarried), in her third pregnancy, within fourteen days of term and without any special effort, complained of pain in the side and cardiac oppression. During labor, just after a pain, she started up in bed with an agonizing pain in her heart, and said she was dying. She became cold and pale and pulseless. She revived for a few minutes and was delivered in about two hours of a dead child. She remained cold and faint, with a small quick pulse, and Linn thought the heart was ruptured. She improved gradually and seemed to be doing very well until the fourteenth day after delivery, when she again complained of a sudden pain in the chest, and she died in a few minutes. A very good illustration accompanying the paper shows an aortitis with rupture into the pericardium. In a woman at this time of life, who had had miscarriage and such a condition of the aorta, the trouble was no doubt due to syphilis. Of the two clinical periods, one corresponds to the rupture of the intima, with which is associated the severe

[1] Fig. 50, p. 327, *Nothnagel's Handbuch*, xv, Bd. ii.
[2] *Denkschriften der Kaiserblichen Akademie der Wissenschaften*, Band iv, Wien, 1850.
[3] *Medical Records and Researches*, London, 1768.

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pain and collapse, from which the patient gradually recovers. Then in the course of three or four days external rupture takes place with sudden death. In some instances, as in Linn's case, the interval may be for fourteen days.

3. **Dissecting Aneurism.**—In ordinary practice and in the work of a general hospital, dissecting aneurism is not very common. There were only two cases in sixteen years at the Johns Hopkins Hospital, where aneurism may be said to be exceptionally frequent. And yet it is a common event, particularly in medicolegal work. I remember well my surprise at the number of cases which the late Dr. Formad used to collect when Coroner's Physician in Philadelphia. A most interesting collection is in Boston, where, in the Warren Pathological Museum, there are twenty cases of dissecting aneurism and rupture of the aorta, most of them collected by the late J. B. S. Jackson. The writer is indebted to Joseph Pratt for getting the details about the cases. Apart from the traumatic instances, there are two groups of cases: the first, occurring in comparatively young persons, results from a rupture of the intima over the middle and external coats, weakened by syphilitic or some other form of aortitis. In the second group, occurring in elderly or very old people, there is extensive endarteritis deformans, and the rupture takes place at the edge of an atheromatous erosion, or an atheromatous intima may be split during a sudden exertion. The most frequent site is the arch and in its ascending portion. But the rupture may occur in any part of the aorta or in one of its main branches.

One of the early cases in which it was recognized was that of George II, who died suddenly of a rupture of the right ventricle. There was in addition in the trunk of the aorta a transverse fissure an inch and a half in length, through which blood had recently passed under its external coat and formed an elevated ecchymosis. As a rule, the blood infiltrates between the layers of the media, sometimes between the media and the adventitia. The extent of the splitting varies from a small area, such as that reported by Nicholls in the case of George II, to a complete separation of the coats of the entire aorta. There are instances on record in which the blood has passed down the crural arteries far into the vessels of the legs. Rupture may take place externally, which is very frequent, into the pericardium, for example, or internally in one or more places into the lumen of the aorta itself. The extent of the circumference of the vessel involved varies very greatly. In some instances only a small section is involved, in others there is a separation of a large part of the circumference, and the vessels may be torn across, although more frequently they are spared. In some cases the intracostal arteries, the cœliac axis, the renal vessels, and superior mesenteric have been torn across. A great majority of the cases of dissecting aneurism prove fatal. The symptoms are those already mentioned in connection with spontaneous rupture of the aorta, a sudden sharp pain, collapse, and death follows in from two to fourteen days from bursting of the aneurism. But in a few cases recovery takes place with an illustration of the most remarkable reparative processes seen in the human body, the formation of a healed dissecting aneurism.

4. **Healed Dissecting Aneurism.**—Shekelton,[1] a Dublin surgeon, first reported cases of this kind, one of the abdominal aorta and the other of the left common iliac. In his first case so similar was the structure to that of

[1] *Dublin Hospital Reports and Communications*, vol. iii, 1822.

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the artery that he was inclined to regard it as an anatomical anomaly, but in the second case the doubt was cleared. Henderson, of Edinburgh, in 1843, reported a remarkable case,[1] in which from just behind the origin of the left subclavian the entire aorta consisted of two tubes. The outer canal communicated with the inner through an orifice into the left common iliac artery. The outer tube did not extend around the entire circumference. Both Shekelton and Henderson appreciated the true character of this remarkable condition. But Hope, in his well-known work on *Diseases of the Heart*, in referring to a case, thought that it was a congenital anomaly, a double aorta. Indeed, when one sees a specimen it is not surprising that

FIG. 47

Healed dissecting aneurism. (After Böstrom.)

this mistake has been made. The best accounts of the condition are given by Böstrom,[2] and by Adami,[3] who has been able to collect altogether 39 cases, among which women were almost as numerous as men. An interesting point is the fact that in a majority of the cases there was no advanced disease of the aorta. This is as we should expect, since, as mentioned in connection with spontaneous rupture, it is due to weakening of the media, and the intima may show little or no atheroma. The site of the primary rupture was in the ascending aorta in 13 cases, below the origin of the left subclavin in 12 cases,

[1] *London and Edinburgh Monthly Journal of Medical Science*, vol. iii, 1843.
[2] *Deutsches Archiv f. klin. Med.*, Bd. xlii.
[3] *Montreal Medical Journal*, 1896, xxiv, p. 945.

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the lower part of the thoracic aorta in 5 cases, in the abdominal aorta and iliac artery 1 case each. As already mentioned, the outer tube may extend the entire length of the aorta and occupy a variable section of the circumference. The branches of the aorta very frequently take origin from the outer sac. A feature which perhaps attracts most attention and has no doubt led to the belief that in these cases a congenital anomaly exists, is the smooth, natural appearance of the outer tube. Rindfleisch showed that a growth of endothelium took place, with the formation, in part at least, of a new intima.

The duration extends over many years. When a student in Toronto, the writer frequently visited the gaol with his old friend and teacher, Professor Richardson, and at intervals they saw there a soldier who had been discharged from the British army soon after the Crimean War for aneurism. He seemed a very healthy man, and there was no evidence of any existing tumor. He died in 1886, and J. E. Graham, who made the postmortem and who reported the case, kindly sent the specimen to me for dissection. There was a small healed aneurism at the third portion of the arch, and from the margin of this sac, just beyond the left subclavian, the aorta formed a double tube. There was little question that this had lasted for more than thirty years from the time of his discharge from the army with symptoms of aneurism.

SACCULATED ANEURISM.

As the great majority of cases of sacculated aneurism in medical practice affect the aorta, we shall deal with the disease as it is met with in this vessel. For convenience of description we may divide the aorta into three parts—the arch, the descending and the abdominal portions:

Aneurism of the Arch of the Aorta.—As already mentioned, this part of the vessel may be uniformly dilated, but it is much more common to have one or other portion involved in a saccular aneurism situated in a sinus of Valsalva, the ascending or the transverse portion of the arch.

Aneurism of a Sinus of Valsalva.—Aneurism of a sinus of Valsalva is a common and important variety, met with particularly in syphilitic subjects and in comparatively young men. There may be a pouching of all three sinuses, but more commonly one only is involved. The orifice of a coronary artery may be given off from the sac, and the first part of the vessel may itself be dilated. The aortic ring may become involved and the adjacent semilunar valve may be rendered incompetent. The aneurism may perforate one or other auricle from the right posterior sinus, or into the pulmonary artery or the right ventricle from the left posterior sinus, or from the anterior; or the sac may pass beneath the ring and perforate into the left ventricle itself. By far the most common perforation is into the pericardium; or rupture may take place into the superior vena cava. There are cases in which the aneurism seems to be given off directly at the aortic ring and involve as much of the ventricle as of the sinus.

Aneurism of this portion of the arch has very definite features: (*a*) It is not detected in the wards, but is seen in the dead-house, particularly in connection with medicolegal work. (*b*) It is very often latent, death occurring from perforation before there have been any symptoms. (*c*) It is frequently syphilitic. (*d*) Angina pectoris may be an early feature. (*e*) Aortic insufficiency is a common accompaniment.

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Aneurism of the Ascending Arch.—Perhaps the most common situation for the saccular tumor is from the convexity of the aorta, an inch or so above the valve. The tumor grows freely to the right, displacing the vena cava and the lung, and some of the largest sacs met with originate in this situation. Anteriorly, it appears to the right of the sternum, in the second and third interspaces, and may gradually erode the bone and cartilage, and, passing upward, lifts the sternoclavicular joint and appears as a large, external tumor. The sac may perforate into the pericardium, the right auricle, the superior vena cava, the lung, the right bronchus, or, passing backward, erode the spine.

FIG. 48

Aneurism of the thoracic aorta.

FIG. 49

Aneurism of the subclavian artery.

Aneurism of the Transverse Arch.—Owing to the very small space between the spine and the sternum, the tumor here is restricted in its growth, and is likely to cause early and severe symptoms from pressure, particularly upon the windpipe. The left recurrent laryngeal is involved, and changes in the voice, attacks of dyspnœa, and painful dysphagia are common. Small tumors may cause the most intense symptoms without, indeed, any physical signs. Although in this situation the sac, as a rule, does not grow to such a size, yet there are instances in which the extension laterally has been enormous, producing some of the largest and most chronic types of aneurism. Growth backward may involve the spine, producing agonizing pain.

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Physical Signs.—*Inspection.*—The well-known dictum of Jenner may be taken as text: "More mistakes are made by not looking than not knowing." A majority of aneurisms of the thoracic aorta present suggestive features to the eye, but the inspection must be made with care. A good light, good eyes, a bare chest, and system are indispensible. There are dark consulting-rooms in which it would be impossible to see the slight throbbing to the right of the sternum or the general diffuse heave of the manubrium. Even in a good light one may look directly at a pulsation and not see it. The point of view is everything, and it is best to examine the patient on a revolving stool, which can be turned easily so as to get the effect of the light falling at different angles. Good eyes are the physician's best tools, but it is not merely acuteness of vision, though this is important, but it is the educated, seeing eye, which is only to be had by careful training.

"Strip to the buff" is the rule. If the shirt and undershirt are tucked up to save time, the all-important area above the level of the second rib may be covered. More than once it has happened in the writer's experience to have the sought-for diagnosis stare at the astonished doctor from the first or second interspace or the supraclavicular region. System is most important: apex region first, then along the sternal margins, the sternal notch, the supraclavicular fossæ, the state of the neck, the superficial veins, the skin, the larynx, the face, eyes, pupils, the epigastric region, all these in quick succession in a preliminary survey, and then anything which attracts attention may be looked at in more detail. Turn the patient and examine the back, particularly the interscapular areas. If not done in order as a routine, the chances are that it will be forgotten as the interest increases in other parts of the examination, and perhaps the diagnosis may be missed altogether. Certain cases make an enduring impression on one. In 1888 the writer saw, at the Girard House in Philadelphia, a man with orthopnœa, a greatly dilated heart with an unusual widespread impulse in the lower sternum and adjacent parts. There was a loud, diastolic murmur, and the whole trouble had been attributed to aortic insufficiency. But there were very puzzling features in the case, which need not here be discussed. After finishing the examination in front the patient's back was turned to the light, when the diagnosis was instantly seen in the form of a prominent pulsating tumor in the left interscapular region, which had been overlooked. The writer on several occasions has missed the diagnosis by carelessness in the routine examination. In a patient named McKinley, very well known to a succession of classes at the Johns Hopkins Hospital, when first seen at the out-patient class, we were so interested in the physical signs in the front of the chest, which were those of a very obscure heart trouble, that we forgot to look at his back. In the ward the House Physician made the diagnosis for us on inspection of the patient's back. There is no disease more conducive to clinical humility than aneurism of the aorta. Mistakes occur with the most careful and the most skilful. Sometimes the diagnosis is beyond our art; more often it is not made because of the carelessness that so easily besets us in our work. The confession of the great Pirogoff always seems to me most touching: "There are in everyone's practice moments in which his vision is holden, so that even an experienced man cannot see what is nevertheless perfectly clear, at least I have noticed this in my own case. An overweaning self-confidence and preconceived opinion, rarely a weariness, are the causes of these astonishing mistakes."

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Face.—The subjects of aneurism are geneally robust, vigorous-looking young or middle-aged men, with what is sometimes called the cardiovascular facies. Marked suffusion of the face is common when the aneurismal sac presses on the veins near the heart. The conjunctivæ may be dusky and infiltrated, and occasionally there is cyanosis. These features of venous compression are not, however, so common in aneurism as in tumor. Occasionally the congestion of the veins may be unilateral.

Inspection of the face gives us the interesting features supposed to be associated with pressure on the cervical sympathetic. Of these, inequality of pupils, *anisocoria*, is the most common. This is present in a very considerable number of cases, and may be due to three causes: (1) When the cord of the sympathetic in the neck is irritated there is contraction of the pupil on the affected side; when there is complete paralysis there is dilatation. Associated phenomena of sympathetic irritation are flushing, unilateral sweating, and drooping of the eyelid. (2) Cecil Wall and Ainley Walker have brought forward evidence to show that this anisocoria is due more often to local vascular conditions The size of the pupil is influenced very largely by the state of turgescence of the vessels. With low blood pressure, large pupils, with a high pressure, contracted pupils, are associated; and these authors think that the anisocoria met with in aneurism is associated with unilateral change in the blood pressure. In 26 consecutive cases of inequality of the pupils in thoracic aneurism they found that there was nearly always a relation between the state of the pupils and the arteries. Where the temporals or radials were small the pupil was large. Experimentally, too, they found that obstruction of carotid vessels in the neck was always associated with a large pupil. In one case of aneurism at the root of the neck on the right side, in which the pupils were equal, distal ligature of the common carotid was followed by enlargement of the right pupil, and an operation on the carotid is reported in which this same sequence followed. In the majority of individuals, pressure on the carotid on one side is followed by enlargement of the pupil. This study gives a very rational explanation of the phenomenon, and removes a very serious difficulty, namely, that very often pupil changes are found when anatomically the aneurism has no connection whatever with the sympathetic. (3) In a certain number of cases the inequality of the pupils is a parasyphilitic manifestation associated with the Argyll-Robertson phenomenon and absent knee-jerks.

Inspection of the neck may show great engorgement of the face on one or both sides, absence of the carotid pulsation on one side, sometimes enormous distention of the right jugular sinus, and in the aneurism of the arch or of the innominate arch together, pulsation of the tumor itself is visible just above the sternum or the sternoclavicular joint. An interesting feature sometimes seen is the visible *tracheal tugging*, a systolic retraction of the box of the larynx, and of the tissues of the root of the neck along the line of the windpipe which may show a lateral deviation.

Arm and Hand.—Sometimes there is swelling of both upper extremities. Particularly is this the case in the aneurism of the ascending aorta, which has grown to the right and compressed the superior vena cava. Much more commonly the arm on one side is congested with enlarged veins, less commonly cyanosis. Pallor and sweating may be present in one arm only. A very interesting feature is the unilateral clubbing of the fingers in thoracic aneurism, of which the writer has seen two cases, one on the right side and

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one on the left. It is associated with peripheral stasis. Groebel, of Nauheim, has reported several cases.

Skin of Chest.—Distention of the veins over the shoulder and pectoral region is common. A network of distended veins may be marked on the right side above the third rib. Very great enlargement of the mammary veins is not so often seen in aneurism as in tumor compressing the superior vena cava. The whole front of the chest may be occupied by large plexus of vessels communicating with the epigastric veins and all the well-known features of obstruction to the blood entering the auricle from above.

Pulsation.—Three sorts of pulsation may be seen in the chest: (*a*) A general shock, such as is present with violent throbbing of the heart, of an aneurism, or of a pulsating aorta. In great hypertrophy of the heart and dilatation of the vessels with marked anæmia, the front of the chest is lifted and jarred with each impulse, often the subclavians throb, and there is a pulsation in the suprasternal notch. Even without organic disease of the heart, as, for example, in cases of Graves' disease, neurasthenia, and severe anæmia, this diffuse throbbing, particularly when associated with marked pulsation of the subclavians, may lead to the diagnosis of aneurism. The shock may be so pronounced as to jar the bed.

(*b*) A diffuse impulse localized over certain parts of the chest and quite different from the general thoracic shock. Usually limited to one side of the chest, to the right mammary or subclavicular regions, it may occur, as is well known, with pleural effusion, gaseous or liquid. There are remarkable instances in which this diffuse pulsation of one side of the chest has occurred without any very obvious cause. Sailer has reported such a case in a Russian Jew, aged twenty-six years, with a normal but not very vigorously beating heart and with marked throbbing of the abdominal aorta. There was a slight though distinct visible systolic pulsation of the whole right side of the thorax, perceptible also on palpation. This sort of throbbing may occur in anæmia and be most deceptive, as in the case reported by A. R. Edwards, in which over the lower left chest there was a diffuse pulsation extending horizontally from the angle of the left scapula into Traube's space and the epigastrium—"the pulsation was vigorous and distinctly expansile to both the eye and the hand." A systolic bruit was heard over it. Naturally the case was regarded as one of aneurism of the thoracic aorta. The postmortem showed moderate arteriosclerosis of the aorta, but no aneurism. Lafleur reported a very similar case with pulsation in the same region, and in addition paralysis of the left vocal cord. And lastly, in chronic mediastinitis there may be a most deceptive pulsation simulating that of aneurism. In 1902 there was under the care of the writer for some months, a patient aged fifty-nine years, who had increasing dyspnœa, cough, and some pain in the chest; the fluoroscope showed an indefinite shadow to the left of the sternum. The voice was a little cracked, the arteries were thickened, and in the second right interspace extending toward the axilla was seen a diffuse impulse, very indefinite, when the breath was held. Taken in conjunction with other symptoms and a slight tracheal tugging, naturally a diagnosis of aneurism was made. W. T. Howard, of Cleveland, who made the postmortem, found a remarkable condition of chronic mediastinitis.

(*c*) *The punctate, heaving, true aneurismal impulse*, which is of a totally different character, localized, and when of any extent visibly expansile. It is first of all most important to recognize the regions in which the cardio-

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vascular impulses may be visible. The apex beat in the fifth interspace and an impulse of the right ventricle in the left costoxiphoid angle are seen over the hearts of thin-chested, healthy persons. Other impulses which must not be mistaken for aneurism are the following: (1) The throbbing of the conus arteriosus in the second left interspace—very common in young persons and in thin chests, and seen particularly well during expiration. (2) Pulsation of the heart in the second, third, and fourth interspaces, extending as far out as the nipple line in cases of sclerosis and retraction, from any cause, of the upper lobe of the left lung. (3) Heart pulsation in the second, third, and fourth right interspaces in connection with similar conditions of the right apex. (4) Effusion in either side of the chest may so dislocate the heart that there is a marked impulse at or outside the nipple line on either side. (5) Throbbing subclavians seen in the outer half of the infraclavicular regions, usually bilateral; this is met with in thin-chested persons, in neurasthenia, in early tuberculosis, and in anæmia. Sometimes it is unilateral, and when accompanied with a thrill and a murmur it may form a mimic or phantom aneurism. Samuel West[1] has reported 8 cases of this kind. (6) In the back part of the chest visible pulsation is nearly always aneurismal; but occasionally, in Broadbent's sign the tugging may be so limited and localized in one interspace that it simulates pulsation, but palpation easily corrects this.

Palpation.—Over a blood tumor connected with the aorta and close to the heart, three things may be felt: (1) *The true aneurismal impulse.* To appreciate its character one must understand that this is identical with the cardiac impulse, and to learn to recognize it one should practise carefully the palpation of an actively beating apex. The remarkable vigor and intensity, the impossibility of resisting it, the closeness under the fingers with the definite expansile quality, are its important features. Of course, these are only appreciated when the aneurism reaches the surface, but even when the sac itself cannot be palpated there may be communicated to the chest wall a forcible heave which is entirely different in sensation from the ordinary shock. In the deep-seated tumor beneath the manubrium this may sometimes be appreciated best by bimanual palpation—one hand upon the spine and the other forcibly compressing the sternum. The communicated shock or jar which is felt over the chest in a case of hypertrophied heart or a throbbing aorta is diffuse, without localization, without any punctate, heaving quality and without that sense of forcible expansion directly beneath the fingers which is so characteristic of the cardiac and the aneurismal beating (2) Over the aneurismal sac near the heart may be felt the shock of either a thudding first sound or, what is much more common, the sharp flap of the second sound. The latter is of great diagnostic importance, and may sometimes be felt by the slightest application of the finger to the sac as a snapping, short shock. (3) *Thrill:* A marked vibratory thrill may be felt, usually systolic in character, much more rarely diastolic and not often double. Thrill is not a special feature of aneurism of the thoracic aorta, and a great majority of cases are without it. It is relatively more common in aneurism of the abdominal aorta. A diastolic thrill is exceedingly rare.

Tracheal Tugging.—When the sac is adherent to the windpipe, with each systole the larynx may be slightly drawn down, and if the finger be placed

[1] *St. Bartholomew's Hospital Reports*, 1880, vol. xvi, p. 119.

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upon it, or if the windpipe is stretched, a slight tug may be felt. This very valuable sign, first described by Surgeon-Major Oliver, is present in a large proportion of all cases of aneurism of the arch when it is in contact with the windpipe. Occasionally it is present in great dilatation of the aorta and in tumors. To elicit this important sign Oliver gives the following directions:

"Place the patient in the erect position, and direct him to close his mouth and elevate his chin to almost the full extent; then grasp the cricoid cartilage between the finger and thumb, and use steady and gentle upward pressure on it, when, if dilatation or aneurism exists, the pulsation of the aorta will be distinctly felt transmitted through the trachea to the hand." It is often visible as well as palpable.

Inequality of the radial and carotid pulses is a very common feature in aneurism. Usually the radial pulse on the one side may be slightly retarded or very much smaller. The carotid may be extremely feeble or obliterated, an event less common in this vessel than in the radial. The right pulse is more frequently smaller than the left. The inequality is most commonly due to involvement of the innominate in the sac with narrowing of its orifice. On the left side the subclavian, with or without the carotid, may be involved in the sac. Either subclavian may be compressed outside the sac. The radial may be smaller on the side opposite to that in which the sac is prominent. Thus a small radial on the left side with a projecting sac from the ascending aorta on the right side may be due to an atheromatous narrowing of the orifice of the left subclavian, or there may be a small secondary aneurism.

It was Harvey, I believe, who first noted the change of pulse in aneurism. In Chapter III of the *de Motu Cordis* he describes the following case: "A certain person was affected with a large pulsating tumor on the right side of the neck, called an aneurism, just at that part where the artery descends into the axilla, produced by an erosion of the artery itself, and daily increasing in size; this tumor was visibly distended as it received the charge of blood brought to it by the artery with each stroke of the heart; the connection of parts was obvious when the body of the patient came to be opened after his death. The pulse in the corresponding arm was small in consequence of the greater portion of the blood being diverted into the tumor and so intercepted."

The pulse may be imperceptible at the wrist and just felt in the brachial, or a very feeble impulse may be seen or obtained by the sphygmograph when nothing is felt by the finger. There are cases in which no pulsation is felt in any of the arteries of the head or of the upper extremities, generally instances of large aneurism of the transverse arch. It is much more rare to meet with obliteration of the pulse in the abdominal aorta or in the femorals. The writer reported one instance in which this interesting condition was present. Absence of the pulsation in a vessel does not necessarily mean that the orifice at the main trunk is obliterated. Feebleness of the pulse on one side may be due, as Harvey suggests, to the diversion into the tumor of the greater portion of the blood, and in the case of a very large sac the force of the cardiac systole may be entirely absorbed and an intermittent converted into a continuous stream.

Blood Pressure.—For several years at the Johns Hopkins Hospital the blood pressure was compared in the vessels of the two arms in cases of

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thoracic aneurism, and not infrequently valuable information was found in the great reduction on one or other side. Naturally it shows best in cases in which the sphygmograph or the finger shows feebleness of the pulse on one side. O. K. Williamson has made a very careful study of this condition in 30 cases and finds that while the arterial blood pressure in aneurism is either normal or slightly above normal, in a majority of cases of thoracic aneurism there is a marked difference in the blood pressure in the two arms, and when this is greater than 20 mm. it is a point in favor of aneurism. He finds the sphygmomanometer much more sensitive than the finger.

Percussion.—When the aneurism reaches the chest wall impairment of resonance shading to flatness is a common physical sign, detected most commonly to the right of the sternum, upon the manubrium, to the left of the sternum in the subclavian and mammary areas, and in the left interscapular region behind. When the sac is closely surrounded by a lung the impairment of resonance may be very slight and only brought out on deep percussion. In large tumors the compression of the lung may lead to shades of tympanitic notes.

Auscultation.—Over an aneurismal sac what one hears will depend very greatly upon the degree of lamination with fibrin and the state of the aortic valves. Usually the heart sounds are transmitted loudly into the sac, the first dull and thudding, the second clear, ringing, and accentuated, relatively louder, as a rule, than the first. This diastolic sound may be the only one audible, and when present is a very valuable diagnostic sign. Adventitious sounds are not always heard. It is surprising, indeed, in how many aneurisms a murmur is not heard. A systolic bruit is common, and it may be transmitted to the vessels of the neck. The diastolic murmur is less frequently heard, and is present when the aortic valves are insufficient or the ring dilated. Sometimes it is caused in the very large sac itself. A to-and-fro double murmur is not uncommon. A continuous humming-top murmur, with systolic intensification, is present when the sac has opened into one of the large vessels or communicates with one of the chambers of the heart.

A systolic murmur is not uncommon over the trachea, and David Drummund pointed out that it may sometimes be heard at the open mouth.

State of the Heart.—Large sacs of the arch displace the heart downward and to the left, and cause it to assume a more transverse position in the chest. This is usually very well seen in the *x*-ray pictures. A very large aneurism growing downward may gradually dislocate the heart and occupy its position, as in the remarkable case reported by Gee. Aneurism of the descending thoracic aorta growing forward may flatten the heart somewhat and give a widespread and very diffuse sort of pulsation in the cardiac area. As a rule, the heart is not enlarged. With the co-existence of aortic insufficiency, dilatation and hypertrophy of the left ventricle are present, and associated conditions, such as arteriosclerosis of the small vessels and contracted kidneys, may cause hypertrophy. But, as a rule, the heart is not enlarged in aneurism of the aorta. Yet occasionally, without any obvious reason, the heart may be voluminous. The writer reported the case of a man aged forty years, with a large saccular aneurism of the descending aorta, in whom the signs of hypertrophy of the heart during life were very marked. At postmortem the organ was found to be greatly enlarged. There was no valvular disease. The left ventricle was much dilated and

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hypertrophied, the chamber measuring, from aortic ring to apex, 12 cm. and the walls from 15 to 20 mm. in thickness.

Symptoms.—*Of aneurism of the aorta in general:* In many cases the condition is *latent.* Those who have seen much medicolegal work appreciate the great frequency of sudden deaths from this cause in apparently healthy individuals. The latent aneurisms are the small, rapidly growing sacs in or just above the sinuses of Valsalva. The small, dissecting aneurisms with rupture, more rarely the ordinary aneurism of the arch reaches a considerable size without symptoms or physical signs. It seems scarcely credible, and yet an aneurism of the arch may penetrate the chest wall and form a tumor the size of the top of a lemon without the patient suffering any serious inconvenience.

The symptoms and physical signs of thoracic aneurism are to a certain extent antagonistic. A patient with the most characteristic physical signs may have no symptoms; one with every symptom may have no physical signs. Hence, Broadbent's useful division into *Aneurism of Symptoms* and *Aneurism of Physical Signs.* As a rule, both features are combined. The symptoms may be considered under the three groups, functional, symptoms caused by compression, and certain special features.

(*a*) *Functional.*—A sac of moderate size interferes little, if at all, with the work of the heart, so that enlargement does not necessarily occur, and when present is usually the result of aortic insufficiency, relative or valvular. Palpitation of the heart, and irregular, unpleasant throbbing may be complained of. During a sudden exertion fainting may occur. Disturbances in the functions of the organs, due to lack of blood supply, are not very common. One carotid may be obliterated without any cerebral disturbances. Hemiplegia, however, may occur. The writer has never seen an instance in which imperfect blood supply to the upper extremities was associated with either paresis or intermittent claudication. But aneurism of the thoracic or abdominal aorta or its branches may be associated with intermittent claudication, and it was in a case of aneurism of the internal iliac that Charcot described first this condition in man.

The *pain* in aneurism is usually attributed to the stretching of the nerves about the aorta and on the sac, but it may be largely due to changes in the artery itself, which has a rich nerve supply. We know that local conditions in the intima may cause agonizing pain, particularly the plug of an embolus. The writer once went into a house for a consultation, a doubtful case, just as the young man had an embolism of the left femoral. He was howling in agony, and could not bear to have the spot touched. Thoma refers to the early pain in the chronic aortitis which leads to dilatation of the arch and attributes it to the involvement of the Pacinian bodies in the adventitia.

Alan Burns, too, called attention to the pain in arterial disease. Attacks of severe angina pectoris may occur in the early stages of aortic aneurism. The cases are met with in comparatively young men who have had syphilis, and the paroxysms may be of great severity and of frequent recurrence. The physical signs may be negative, and it may be a year or more before aneurism is suspected.[1] In other instances there are well-marked signs of aortic insufficiency. A feature of very great interest in certain of these cases

[1] For group of cases, see *Medical Chronicle,* 1905.

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is the complete disappearance of anginal attacks with the use of iodide of potassium.

(*b*) *Symptoms of Compression.*—An aneurism may grow to a large size without causing inconvenience. Whether active symptoms of compression are caused depends on the situation of the tumor and on the direction of its growth. From the ascending and terminal portions of the arch tumors extending laterally are much less likely to interfere with neighboring structures, and the largest tumors arise from these portions. The space between the posterior wall of the sternum and the spine at the level of the aorta is only a few centimeters, so that aneurisms growing from the transverse portion of the arch cause early signs of compression.

The chief symptoms of aneurism are those of tumor, and arise from interference with neighboring parts by compression. The following are the more important structures involved: (1) *Nerve trunks and plexuses:* Pain due to stretching and pressure on the nerves is a common yet a very variable feature. A huge sac may erode the chest wall without causing any serious inconveniences. The pain presents very different characters. As already mentioned, there may be attacks of angina pectoris associated with an aortitis, and the beginning of the formation of the aneurism. More commonly, it is of a dull, heavy character, deep seated, and greatly aggravated in certain positions. It may present the features of a cervicobrachial neuralgia; in other cases, of an intercostal neuralgia of great severity and persistence. Sometimes the pain shoots down the arm, and there may be numbness and tingling as far as the finger tips. Erosion of bones is usually associated with pain of a very intense boring character, but the sternum and adjacent cartilages and ribs may be eroded and perforated without causing any distress. On the other hand, the spinal column when compressed is a source of persistent and terrible pain. Sometimes it is of the well-marked character of nerve-root pains, such as we see in secondary carcinoma of the spine, but in other cases it is different—a deep-seated, boring intense agony only relieved by maximum doses of morphine. These terrible tragedies of pain are most common in aneurism of the lower thoracic and abdominal portion of the aorta. The corresponding skin areas of Head may be sensitive to touch, in the region of the nipple, along the left sternal border, and over the neck.

Compression or irritation of certain nerves may cause special symptoms. Irritation of the *phrenic* may be assocated with hiccough. Symptoms arising from compression of the pneumogastric are not often met with. Some have attributed to this cause the attacks of nausea and vomiting which occasionally occur, and the recurrent dyspnœa, but this does not seem to be very likely.

Pressure on the *sympathetic* has already been considered in speaking of the physical signs. It does sometimes occur with the characteristic features, namely, flushing of one side of the face with increased heat, sweating, dilatation of the pupil, and slight drooping of the eyelid. This is, however, a rare combination. It has already been mentioned that the difference in size of the pupils is most frequently a question of tension in the ophthalmic arteries. Unilateral sweating is probably the most characteristic sign of compression of the sympathetic. This interesting feature, first noted by Gairdner, is usually confined to the sides of the face and neck, toward which the aneurism projects, and more frequently on the right side than on the left. The writer

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has seen it on the side opposite to that in which the aneurism is bulging, but it is not always possible to say how far the sac may extend on either side of the middle line, and it is a very short distance from the aorta to the cord of the sympathetic. The sweating may extend to the arm and side of the chest and the skin of the right hand may be like that of a washerwoman's. Instead of being flushed and of a higher temperature, the skin on the affected side may feel cold and be several degrees lower than the opposite side. The skin of the face may look pale, and sometimes the hand and arm of the affected side is quite pallid.

The Recurrent Laryngeal Nerve.—Pressure on this nerve is a common event in aneurism of the arch, around which the left nerve curves, and it may occur with very small tumors. The right nerve may be involved in a large sac springing from the ascending aorta and the transverse arch. The symptoms caused are very important: (*a*) Alteration in the voice, which has a cracked character, often sufficient to attract the attention. Sometimes the change is very slight, but in others it is most striking. Actual aphonia is rare, although the voice may be reduced to a whisper. Most commonly the voice is that of a unilateral paralysis. (*b*) A peculiar quality of the cough, which becomes ringing, "brassy," or croupy. It differs from the cough of tracheal or bronchial compression, which is dry, harsh, and grating, and is usually accompanied with dyspnœa. (*c*) In rare instances there is painful spasm of the muscles of the larynx and pharynx, and even of the œsophagus. (*d*) Attacks of dyspnœa, which may occur with unilateral paralysis, are more common when both nerves are affected, as they may be by two aneurisms, or in rare instances by an ascending neuritis and extension to the nucleus of the other nerve.

Œsophagus.—Dysphagia is a very common and, with the small tumor from the posterior part of the arch, an early symptom. It is rarely extreme, but it may prevent the patient from taking solid food. Perforation of the œsophagus and fatal hemorrhage may occur without any previous difficulty in swallowing. The results of the compression may be necrosis of the wall without perforation. Ulceration may occur over the point of greatest compression. When the sac perforates directly into the gullet there is fatal hemorrhage; sometimes the orifice is temporarily blocked by a clot.

Trachea and Bronchi.—The most common and characteristic features of aneurism are associated with irritation and compression of the air passages. The condition may at first be mistaken for asthma. *Cough*, one of the earliest symptoms, is due in a great many cases to tracheal irritation, more particularly when the sac is in the neighborhood of the bifurcation. When there is simple compression, anything that lowers the tension in the sac benefits the cough, and ten days in bed may cause its disappearance. On the other hand, the slightest exertion may bring it on. In other cases the cough is due to a tracheitis, and the mucous membrane is found swollen and reddened and there is a great increase in the secretion. There is a difference in the character of the cough in the two conditions. In one it is dry and wheezing, nothing is brought up, but in the other there is a very large amount of expectoration. The peculiar, brazen quality of the cough in aneurism is laryngeal, not tracheal.

Dyspnœa.—Aneurismal dyspnœa presents the following characteristics. In the first place there may be the ordinary shortness of breath associated with the growth of a large intrathoracic tumor, but without any signs of direct

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compression of the trachea. Aneurismal dyspnœa resulting from this cause is infralaryngeal, with all the qualities of this type so thoroughly discussed by Grossmann[1] in his well-known study on tracheal stenosis. All grades of it are met with. In the aggravated cases there is an orthopnœa with prolonged inspiration, often noisy, sometimes with a marked stridor, or a fine sibilant sound. Expiration is shorter and not so noisy. While the difficulty of breathing is constant, there are paroxysms in which the intensity is greatly increased and the patient feels, as Morgagni expresses it, as though a cord was being tightened about the windpipe. Retraction of the tissues at the root of the neck, the epigastrium, and the costal borders is usually present. Gerhardt called attention to the limitation of vertical movement of the larynx in tracheal stenosis: "In spasmodic and stridulous breathing laryngeal movement of less than one centimeter is a certain sign of tracheal or tracheo-bronchial stenosis." Very often these patients are admitted to the hospital in terrible paroxysms, and it may not be easy to determine whether the narrowing is laryngeal or not. If a laryngeal examination can be made it is not difficult, but otherwise it is not at all easy. The cracked voice, the brazen character of the cough, the quality of the stridor, whether over the larynx or lower in the course of the trachea, the degree of movement of the larynx in inspiration, are important points.

Compression of Bronchus.—An aneurism may narrow one or other main bronchus without seriously compressing the bifurcation, or only the branch going to one or other lobe may be involved. This may produce a picture in which the true nature of the disease is obscured. In gradual compression the condition of atelectasis may follow with subsequent sclerosis. This does not often happen to an entire lung, but it may to a lobe or part of a lobe. The narrowing results in retention of secretion and intense bronchitis, sometimes with expectoration of large quantities of muco-pus. Dilatation of the bronchi may supervene, but more common and deceptive is the gradual invasion of the lung tissue itself, so that the organ becomes consolidated, the bronchi filled with pus, sometimes quite inspissated, and the lung infiltrated, perhaps here and there a cavity formation. The whole process resembles tuberculosis, for which clinically the cases are mistaken. There may be areas of consolidation and bronchiectasis in both lungs as a result of tracheal compression. At the Montreal General Hospital the late George Ross used to speak of this condition as "aneurismal phthisis," and the writer has seen four or five cases in which the diagnosis of consumption had been made.

Lung.—The growing sac may push aside the lung and compress the upper lobe without causing anything more than slight atelectasis, expressed clinically by the very important physical sign of feebleness or absence of breath sounds. But the sac may grow directly into the lung, the tissues of which form its actual wall. Under these circumstances, if the sac is small and grows from the terminal part of the arch into the left apex, and if hæmoptysis is present, the case is of course mistaken for one of tuberculosis. The writer saw two such instances in 1907, one at the Royal Victoria Hospital, Montreal, with Dr. John McCrae, the other at the Radcliffe Infirmary, Oxford, with Dr. Mallam. In neither was there any suspicion of aneurism. In both there was fatal hemorrhage. In other instances the aneurism grows into the lung, and in the formation of a large sac repeated small hemorrhages

[1] *Wiener Klinik*, 1890.

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occur. Complete consolidation may follow. There is a specimen in the McGill Museum of an aneurism which occupies a large portion of the centre of the left lung, and which had become obliterated by thrombi.

Bloodvessels.—Considering how close in many cases the aneurism is to the great veins, it is surprising how rare are severe symptoms due to compression of the superior vena cava. The pressure may be exerted on the vena cava itself, on the innominate, or on one of the subclavian veins. It is not very uncommon to meet with congestion of the veins of the neck and head, and sometimes one or other arm is swollen. All this may disappear completely after a copious bleeding or after a week's rest in bed. The small aneurism of the ascending portion of the aorta growing to the right may compress the vena cava very early, even before physical signs are apparent. It is in this situation particularly that the most marked effects of compression from aneurism are seen. Narrowing of the lumen is the most common event, and throughout the course of the disease there is more or less fulness of the veins of the head and upper extremities. Rupture of the aneurism into the superior vena cava is followed by remarkable signs and symptoms, which will be discussed under the section of arterio-venous aneurism. The gradual compression may lead to thrombosis and complete obliteration of the superior cava. Of the 29 cases which the writer collected in a paper on obliteration of this vein, 4 were associated with aneurism. The picture is usually a very striking one, owing to the enormous development of the collateral circulation. This is carried on through a number of channels: (1) If the obliteration is above the point of entrance of the vena azygos, a large amount of blood from the arms and trunk finds its way into this vein through communications of the intercostals with the internal mammaries. (2) Over the surface of the chest the plexus of mammary veins enlarges and the subcutaneous tissues may be swollen, and the entire front of the chest is occupied by a system of greatly distended veins. These may be seen in and beneath the skin forming tortuous channels the size of the finger and converging to two or three large vessels which unite with the epigastrics. On the front of the abdomen are seen large convoluted vessels which empty below into the femoral veins. In some cases the venous plexuses are entirely subcutaneous. In others the veins of the skin itself are dilated and give the general surface a purplish red hue. So distended may the superficial mammary veins become that in the large sinuses thrombi form which may ultimately calcify, forming vein-stones. (3) Extensive communications exist between the deep cervical and the vertebral veins with the intercostals and the whole network of veins along the front of the spine. These communicate freely with the branches of the azygos, or when the orifice of that is obliterated numerous channels are established between the lumbar vessels and the territories of the inferior vena cava.

The *inferior cava* is less often compressed. The *innominate vein* or *one subclavian* may be narrowed, rarely obliterated, causing great engorgement of the hand and arm. The *pulmonary artery* may be narrowed or perforated. Gangrene of the lung has been caused by compression of the vessels. *Compression of the vena azygos* may cause œdema of the chest wall or effusion into the right pleura. The *thoracic duct* may be involved in any part of its course, but symptoms due to this complication are rare. Morgagni noted the great dilatation of the abdominal lymph vessels with varices and lacunæ in a case of aneurism of the thoracic aorta.

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Spinal Cord.—In a few instances the bodies of the vertebræ have been destroyed and the spinal cord directly compressed by the sac, causing paraplegia. Rupture has occurred into the spinal canal. The paraplegia may be due to blocking of the aorta, which causes anemia of the cord such as follows ligation of the vessel experimentally.

Special Symptoms.—*Hæmoptysis.*—Latent tumors growing backward from the transverse arch may rupture into a bronchus or the trachea, causing early and fatal hemorrhages. More frequently there are well-marked signs, and the bleeding may be of very different characters. With pressure and a granular tracheitis, bloody sputa may occur for weeks and gradually disappear. Brisk hemorrhage almost always comes from an open erosion, but it is not necessarily directly fatal. The laminæ may be within the lumen of the trachea, and through small chinks and crevices the sac may "weep" at intervals, or continuously for weeks and months. There are remarkable cases in which in the course of a few weeks numerous hemorrhages occur. T.W. Clarke reports a case of this kind in which sixteen hemorrhages occurred between July 23 and September 15, the amount of blood ranging from a few ounces to 36 ounces at each bleeding, a total of 14 pints in seven and a half weeks. A saccular aneurism was found projecting upward and backward into the upper lobe of the right lung, which incased two-thirds of its extent, occupying nearly the whole of the upper lobe of the lung; into it small bronchi could be directly traced. Rupture occurred into the right pleura. Death may not follow for months or even years. A patient of Dr. Fussell, with aneurism, upon whom the writer lectured in Philadelphia, lived for four years after a severe hæmoptysis. The famous surgeon, Liston, had, in July, 1847, a feeling of constriction at the top of the windpipe and slight difficulty in swallowing. A profuse hæmoptysis, 30 to 40 ounces, nearly killed him. Liston himself suspected aneurism, but neither Watson nor Forbes could discover anything in his chest. He was greatly relieved by the hemorrhage. In October the symptoms returned, but it was not until December 6 that he died in a paroxysm of dyspnœa. The trachea was perforated, but the orifice was blocked by firm laminæ of fibrin. The small tumors growing upward into the apex of the lung on either side may be associated with repeated hemorrhages, and the diagnosis of tuberculosis is usually made.

Modes of Perforation.—1. *External.*—As the sac enlarges, the wall of the thorax is perforated, the tumor appears beneath the skin, and may reach an enormous size. Finally the skin becomes reddened, a spot of necrosis forms, slowly increases, the aneurism at first "weeps," and finally bursts with fatal hemorrhage. Considering the large number of cases in which the chest wall is perforated and the skin eroded, fatal hemorrhage from this cause is comparatively rare. The sac may be very voluminous, as represented in Fig. 50, which shows a negro with an aneurism of the descending thoracic aorta. Lined as it is with firm thrombi, the sac may perforate the skin without any hemorrhage, and the patient may live for months and die of internal rupture. William Hunter reports the case of a man with an aneurism perforating to the right of the sternum, in whom the sac bled for weeks at intervals from an orifice plugged by a coagulum which protruded and retracted with the systole and diastole of the heart. A sudden cough burst out the plug, and "the blood gushed out with such violence as to dash against the curtain and wall, and he died not only without speaking but

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without a sigh or groan." The writer has seen a sac "weep" for months; in one patient it became infected with the *Bacillus capsulatus aërogenes*, and the patient died of a general infection. It is remarkable how much a sac presenting externally may vary with the condition of the patient. Prolonged rest in bed, bleeding, wiring, may reduce the size, and we have had instances in which the external tumor has completely disappeared. Great relief may be obtained by a carefully adapted bandage, but it must not be too tightly applied. Some years ago the writer saw a physician with a very large sac projecting beneath the right clavicle, for the support of which he wore a very ingeniously devised pad. Lancisi refers to a case in which for a tumor in the same region the surgeon ordered a kind of truss to restrain it, but the sac

FIG. 50

Aneurism of the descending thoracic aorta. (Photograph taken by I. C. Skinner, M.D., of Selma, Alabama.)

burst internally. By far the most common site of external perforation is to the right of the sternum. A prominent sac may disappear completely after external rupture (Morgagni).

2. *Perforation into the Trachea or Bronchi.*—Already under the section on hæmoptysis this has been referred to, and it is perhaps the most common of all localities. It usually takes place in the lower third of the tube, and the orifice may be single or double. By pressure the wall is gradually eroded; a small, rapidly growing sac may perforate before there have been any special symptoms; more commonly there is an irritative cough and the characteristic dyspnœa. As already mentioned, the perforation is not necessarily fatal, and the symptoms may be, as in Liston's case, greatly

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relieved by the hæmoptysis. The orifice may be closed by firm thrombi, and months or even years may elapse before final perforation takes place. In one case under the care of the writer there were two perforations, and the patient died of a third one into the œsophagus. The left bronchus is more frequently involved than the right, more frequently, indeed, than the trachea itself.

3. *Rupture into the Lung.*—This has already been discussed in speaking of the pulmonary features. The lung tissue itself may form a large part of the wall of the sac, and it is particularly aneurisms of the terminal portion of the arch and the first part of the thoracic arch that tend to grow into the upper lobe or invade the central portion of the lung. Slight and recurring hæmoptysis may occur, and the diagnosis of tuberculosis is sometimes made. The writer has not met with an instance of fatal hemorrhage unless the sac opened into a bronchus. There may be a very large sac almost completely consolidated within the lung substance itself. A brief reference to the Index Catalogue (both series) under Aneurism gives a good idea of the great frequency of rupture into the trachea, bronchi, and lungs.

4. *Œsophagus.*—This is not so common, and there were only 9 cases among 226 of Crisp's series. The rupture takes place usually by gradual erosion, which has sometimes been preceded by local necrosis and gangrene. Dysphagia usually precedes the perforation, but in small sacs the rupture may take place suddenly in individuals in excellent health. The writer has reported such an instance in a woman, aged thirty-five years who died in syncope. The aneurism was only 5 by 5 cm. in extent, and communicated by a linear slit 1.5 cm. in length with the lumen of the aorta. It is not uncommon to find the œsophagus stretched over the wall of the sac, closely adherent, and the muscular layers much wasted. The cases in which ulceration and gangrene precede the rupture are of special interest, since cancer of the œsophagus may be suspected. In the Index Catalogue, second series, there are 17 cases of perforation of the œsophagus noted. It may take place simultaneously into the bronchus or trachea and the œsophagus. The coats of the œsophagus may be split and the blood pass between them and burst into the stomach, as in a case reported by Frederick Taylor.

5. *Rupture into the Pericardium.*—This is one of the common causes of sudden death in robust, apparently healthy men. Medicolegal records of large cities show the very great frequency of this accident. The perforation may be of a small sac of one of the sinuses of Valsalva, or there is a tear of the intima with a small dissecting aneurism and rupture of the external coat, or the intrapericardial portion of an aneurism of the ascending portion of the arch gives way. The rupture may be pinpoint in size or a large transverse tear. In a few cases a small mycotic aneurism bursts. Death takes place with suddenness. There are instances on record in which the patient has lived for some hours.

6. *Other modes of rupture* are on record—into the anterior or posteror mediastinum, the muscles of the neck, and into the vessels and heart, which will be referred to in the section on Arterio-venous Aneurism.

The conditions under which rupture may occur are important. When the individual is at rest or sleeping the fatal event may happen. More often, the rupture is during some exertion, while straining at stool, or in a scuffle, or while under an anæsthetic. The dangers of coitus were referred to by Morgagni, who says that many patients die in this way.

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FIG. 51

FIG. 52

Side and front view of a thoracic aneurism just beginning to "point."

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Pleura.—Hydrothorax is not very uncommon, and may be a pressure effect on the azygos veins, and it is more frequent on the right side than on the left. It may complicate the diagnosis, and sometimes recurs repeatedly. The bloody serum may be present as an effect of pressure on the veins. Acute pleurisy, usually tuberculous, may be a terminal event. In a few cases aneurism has been complicated by empyema.

Descending Thoracic Aneurism.—Aneurism of this portion presents a few special features. It is rarer than in the abdominal aorta. If we add the statistics of Crisp, Lebert, and Myers, this portion was involved in 49 against 159 of the ascending, 113 of the arch, and 83 of the abdominal aorta. It was only involved in 3 out of 64 cases of aneurism of the aorta among 2200 autopsies at the Johns Hopkins Hospital.

Symptoms.—There may be no symptoms whatever; the first indication may be a sudden syncope from internal hemorrhage, vomiting of blood or hæmoptysis. Three out of the 14 cases described by the writer were latent. A second feature is the intensity and the peculiar character of the pain. Owing to the close relation of the aorta to the spine and the frequency with which the tumor grows backward, pain in the back and along the sides from pressure on the nerves is usually *the symptom* of the case. Erosion of the spine to an extensive degree may occur without pain, but this is rare. Some of the patients are never without it for a moment, except when under the influence of morphine, of which one patient took for a long period as much as between 30 and 40 grains a day. There may be nothing in the case but the *pain.* Perhaps to the left of the spine there is heard a soft systolic murmur, or there are feeble breath sounds in the left lung, but it may be months before there are any physical signs. The third special feature is the prominence of the pulmonary symptoms due to pressure either on the lung itself or on the main bronchus. Hemorrhage occurred in only 3 of 14 of the writer's cases; it may be due to a direct weeping through the lung tissue, or it is a terminal hæmoptysis due to perforation of a bronchus. The whole lung may be compressed by an enormous aneurism, or the bronchus may be blocked with the production of purulent bronchiectasis, and the patient may present the symptoms of extensive destruction of the lung. And lastly, some writers have referred to pressure on the gullet as a special feature of aneurism of this part. It was present in only two of the writer's cases and in only one did rupture take place into the œsophagus. The tumor may grow to an enormous size, as in the famous case[1] in which the patient lived for twelve years and the greater part of the left chest was occupied by a non-pulsating tumor.

Abdominal Aorta.—The *incidence* varies in different localities. Sixteen cases occurred among about 18,000 admissions to my wards. The ratio of abdominal to thoracic aneurism was 1 to 10. Among 2200 autopsies at the Johns Hopkins Hospital there were 11 instances of aneurism of the abdominal aorta. The Guy's Hospital figures have been collected by the late J. H. Bryant for the years 1854–1900; among 18,678 necropsies, there were 325 cases of aneurism of the aorta, of which 54 (or 16 per cent.) were of the abdominal portion. Males are much more frequently attacked than females. Only 2 of the writer's 16 cases were females, and all statistics indicate this infrequency in women, a point to be borne in mind, as the

[1] *Deutsch. Arch. f. klin. Med.*, Band xix.

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throbbing aorta is so much more common in them. A majority of the patients are young men. In 63 per cent. of Bryant's series they were under forty years of age, and in 2 the disease began before the twentieth year.

It is most frequent in the upper portion of the abdominal aorta, and it is usually of the saccular form. Rupture into the retroperitoneum is common, forming the diffuse or false aneurism, which may reach a colossal size. A huge sac may occupy one-half of the abdomen and project in the back, forming a tumor the size of the head.

Symptoms.—In no situation are the symptoms of aneurism so obscure, and even when pulsation is present the diagnosis is not easily reached. This is well brought out by Bryant in the analysis of the Guy's Hospital statistics: "A correct conclusion during life as to the nature of the disease was arrived at in 18 only out of the 54 cases on which this lecture is based, an analysis showing that an abdominal tumor was detected in 31, pulsation in 35, expansile pulsation in 8 only, and in 26 a systolic murmur. Incorrect diagnoses of a variety of diseases were made, including malignant tumors lying in front of the aorta, renal calculus, lead colic, spinal caries, sarcoma of the kidney, nephritis, perinephritis, pneumothorax, pleuritic effusion, epithelioma of the œsophagus, malingering, chronic intestinal obstruction, etc."

Pain, usually the first indication, remaining throughout the special feature and reaching an intensity not met with in any other disease, presents three features of importance. It is usually of a constant, dull, boring character, particularly when the aneurism has eroded the spine. There may be paroxysms of the greatest intensity for months before a diagnosis is made. And lastly, when the aneurism ruptures into the retroperitoneal tissues, the pain with other features may give to the case the characters of the acute abdomen. The writer knows of at least four cases in which the operation for appendicitis was undertaken. Nausea and vomiting may be early and severe symptoms. In one of the cases there was great dilatation of the stomach due to pressure upon the duodenum. In another there was great dilatation of the œsophagus owing to pressure at the cardiac end of the stomach. The aneurism may rupture into the stomach, duodenum, or colon, into the retroperitoneal tissues, which is the most common mode, or pass upward and rupture into the pleura. The peritoneum, the bladder, or the inferior vena cava may be perforated. Embolism of the aorta below the sac may occur, or one femoral may be blocked with the result of gangrene of the leg. The writer has not found a case of external rupture. Embolism of the superior mesenteric artery may occur with infarction of the bowel.

ARTERIO-VENOUS ANEURISM.

A communication between artery and vein with or without an intervening sac. In the one case the term *aneurismal varix* is applied, and in the other, when a sac is formed between the two vessels, *varicose aneurism*. Although chiefly a surgical affection, met with in the peripheral arteries, it occurs in the internal vessels and has important medical bearings.

William Hunter, in 1757, described a particular species of aneurism following the simultaneous opening of an artery and a vein, in consequence of which the latter became dilated and varicosed, and had a pulsatile, jarring

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motion with a hissing noise. He described several cases which occurred from unskilful venesection at the bend of the elbow. The observation was not new; from the time of Galen it has been known that aneurism might follow unskilful venesection at the bend of the elbow, but Hunter recognized it as a special form. The monograph of Breschet[1] and the work of Broca[2] are of great value; indeed, there is not a better description in literature than that given in the latter.

Traumatic.—These cases have a surgical rather than a medical interest. While in the internal vessels the communication is usually direct, in the larger external trunks there is more often the intervention of a sac. Formerly, venesection at the bend of the elbow was the common cause, and the communication existed between the brachial artery and the vein. Now the cases are chiefly the result of stab wounds and of bullet wounds. Military surgeons state that with modern bullets the lesion has become more common. The experience of the South African War is given by W. F. Stephenson[3] in a Government Report, and of the Russo-Japanese War by Siago.[4] The recent work of Matas[5] and the extraordinary technique in arterial surgery developed by Carrel (Rockefeller Institute Publications, New York) should lead to greatly improved results.

The vessels most commonly involved are the femorals, subclavians, axillaries, brachials, and popliteals. So much higher is the arterial than the venous blood pressure, that when an artificial communication exists between vein and artery, the former with its branches becomes permanently distended. The obstruction offered to the free return of blood makes the distention of the collateral veins still more marked. The orifice of communication may be small and slit-like or oval, and, as already stated, a sac may exist between the two vessels. In many cases the communication is direct. The anatomical changes are chiefly in the veins, which become greatly enlarged, varicosed, with thickened walls, and frequently present flakes of atheroma in the intima.

The three distinguishing features of this aneurism are: (1) The swelling of the part caused by the distention of the veins. When only the deeper vessels are involved, they may not be visible externally, but, as a rule, large varicose vessels are to be seen. In the case of arterio-venous aneurism of the femorals or iliacs the engorgement of the veins may be enormous. In no condition do we see such huge saccular dilatations. In the annexed figure one of these is shown forming a large tumor just above Poupart's ligament. In the veins and in the large venous sinuses pulsation may be visible, but, except close to the arteries, it is not forcible. (2) On palpation a vibratory thrill is felt, of maximum intensity over the position of the orifice, but widely diffused, and in the case of an aneurism of the axillary vessels, to be felt as low as the palm of the hand, and in the case of an aneurism of the femoral vessels, to be felt as low as the foot, and even to the crown of the head. In the large bunches of subcutaneous veins, the calcified walls and occasionally phleboliths may sometimes be felt. When a sac intervenes between the artery and the vein, it may be felt, and presents aneurismal pulsation, forcible

[1] *Mémoires de l'Académie de Médecine*, 1833.
[2] *Des Aneurismes*, 1856.
[3] *On the Surgical Cases, etc.*, 1905.
[4] *Deutsch. Zeit. f. Chir.*, Band lxxxv.
[5] *Journal of the American Medical Association*, 1902, vol. xxxviii, p. 103.

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and expansile. (3) On auscultation there is heard everywhere over the aneurism and up and down the limb a "bruit de diable" of great intensity. An interesting point is the fact that one of the earliest instances recorded of auscultation was in a case of varicose aneurism reported by Mr. White, a surgeon at York, in a letter to William Hunter. He states, "On applying my ear to the tumefied basilic vein, the pulsation, tremulous motion, and noise are distinctly perceived." The murmur is continuous, with systolic intensification.

The condition may remain stationary for years. Spontaneous healing does not occur. There may be progressive increase in the veins, leading to enormous varicosity and to great disability, and it is for this that relief is sought. Rokitansky reports a case of a man, aged sixty-two years, who thirty-three years before had had a bullet wound in the left shoulder. There were uneasy feelings in the arms at times, but only for two years had it increased greatly in size and become blue-red and œdematous. This progressive enlargement of the veins is really the chief danger. At the age of fifteen

FIG. 53

Arterio-venous aneurism of the iliac vessels.

years a young man fell and forced a lead-pencil into his axilla. This was followed by a gush of blood, and in a few moments the arm began to swell and became black and blue to the wrist. He gradually got better, but there was always a swelling in the armpit and infraclavicular region. It did not, nowever, interfere with his work or exercise. Ten years after, when the writer saw him, he had well-marked signs of arterio-venous aneurism of the axillary vessels. He was athletic and had rowed in races. He has been seen at intervals since, and there is practically no change in the arterio-venous aneurism. He subsequently served in the South African War, and was invalided for aneurism of the shoulder! The writer heard of him last in 1901, which was twenty-three years after the accident. Broca mentions two interesting circumstances: the greater growth of the limb below a femoral aneurism of this kind, and the increased growth of hair on the skin, both the result of the venous engorgement.

Internal Arterio-venous Aneurism.—While rare, this form is of great interest.

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1. **The Aorta and Superior Vena Cava.**—This gives a very remarkable picture. One morning, at the hospital of the University of Pennsylvania, a Chinaman, aged forty-eight years, was admitted in a condition of extreme dyspnœa, with the skin of the face and arms cyanosed, the eyes suffused, and the whole upper part of the body engorged and œdematous. He presented an extraordinary appearance on account of the contrast between the upper and lower part of the body. The writer had never seen a similar picture. The case, which was under the care of his colleague, Pepper, excited a great deal of interest. The most striking physical signs were: a loud thrill over the præcordia, a continuous "humming-top" murmur, with marked systolic intensification, which was heard best over the base, and was transmitted into the vessels of the neck and down the arm as far as the elbow. The patient lived for two weeks, with extreme orthopnœa and an increase of the œdema of the upper part of the body; so intense was the infiltration of the blood-vessels of the conjunctiva that blood oozed. The writer made the autopsy with Crozer Griffith, who, in conjunction with Dr. Pepper, has reported the case very fully.[1] A small aneurismal sac of the ascending aorta had perforated the superior vena cava. A second case at the Johns Hopkins Hospital, in 1899, presented an almost identical appearance.[2] The patient's face was enormously swollen and blue looking, like a man who had been strangled. There was the same extraordinary contrast between the upper and the lower part of the body. In the second right interspace was heard a loud, continuous murmur, with marked systolic intensification. The patient had had syphilis two years before, and although there were no signs of aneurism, there could be very little question as to the nature of the trouble.

The first report of a case of this kind was by John Thurnam,[3] whose paper on these internal arterio-venous aneurisms was the first and is one of the best in literature. A man aged forty-one years, had sudden swelling and cyanosis of the upper part of the body, with a loud "bruisement," like the vibration of a string, on the right side of the sternum. At postmortem an aneurism of the aorta was found to have perforated the superior vena cava. Pepper and Griffith collected 28 cases of this lesion, and there have been a good many reported since the appearance of their paper. The symptoms are quite distinctive: (1) cyanosis, œdema, and distention of the veins of the upper part of the body, with signs of obstruction in the tributaries of the superior vena cava; (2) suddenness of the onset of the symptoms; (3) evidence of the presence of a tumor in the thorax; (4) the existence of a murmur characteristic of a communication between an artery and a vein.

2. **Aorta and Pulmonary Artery.**—This is rather more frequent, and the condition has been carefully studied by Frederick Taylor and Gairdner; Kappis,[4] from Baümler's clinic, has collected 30 cases. The symptoms are not unlike those of perforation into the superior vena cava and are characterized by a sudden onset with cyanosis and œdema, which, however, are not so accurately limited to the upper half of the body, as in the cases of perforation into the superior vena cava. Signs are usually present of aortic aneurism. A thrill is felt over the base of the heart, and there is a loud humming-top murmur, with maximum intensity to the left of the upper part of

[1] *Transactions of the Association of American Physicians*, 1890, vol. v.
[2] Notes on Aneurism, *Journal of the American Medical Association*, June 7, 1902.
[3] *Medico-Chirurgical Society's Transactions*, 1840, vol. xxiii, p. 323.
[4] *Deutsch. Arch. f. klin. Med.*, Band xc, 1907.

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the sternum. Thurnam has reported a case of perforation of an aneurism into the right ventricle, which had a murmur of the same character in the second left intercostal space.

Perforation of an aneurism into one of the branches of the pulmonary artery gives rise to a similar murmur. In a case admitted to the wards in 1901, with aneurism of the thoracic aorta, there was a feeble thrill and very loud continuous murmur occupying the entire cardiac cycle, with marked systolic intensification. This was heard best to the right of the sternum. The aneurism was found to have compressed the right lung, which formed the posterior wall of the sac into which one of the main branches of the pulmonary arteries had opened.

3. **Abdominal Aorta and Inferior Vena Cava.**—This is not so common. Thurnam reports 3 cases in his paper, in all of which the perforation had taken place from an aneurism. In 1 case in J. H. Bryant's series at Guy's Hospital the vena cava was perforated. As a rule, the symptoms are well defined, namely, those of aneurism of the abdominal aorta, with sudden onset of swelling and cyanosis of the lower extremities, and œdema of the lower half of the body. The characteristic humming-top murmur is heard over the tumor.

DIAGNOSIS OF ANEURISM.

From Dynamic Dilatation of the Aorta.—That the throbbing, distended aorta, the condition of preternatural pulsation, as Allan Burns calls it, may lead to diagnosis of aneurism is an observation that dates from the time of Morgagni. It is met under the following conditions.

1. **Aortic Insufficiency.**—In young persons the degree of dilatation caused by the propulsion of a large volume of blood from a powerfully acting heart may be extraordinary. It is not very uncommon to see a slight throbbing of the aorta to the right of the sternum in these cases. Occasionally in a young man, when the insufficiency is extreme, and if anæmia is present, the degree of throbbing and the extent of visible impulse in the second and third, or in the first and second right interspaces almost compels the diagnosis of aneurism; and yet postmortem the aorta may not be beyond the ordinary size. Much more commonly the mistake arises from the throbbing and dilatation of the innominate and the right carotid. Corrigan calls attention to this in his original paper: "So strong were the pulsations for years in the region of the arterio-innominate that until the examination after death there was never even a doubt expressed that the case was not aneurism." Many cases of this sort have gone into literature as aneurism. In 1886, Hare[1] reported an interesting case of this kind. A girl of seventeen had had repeated attacks of rheumatic fever, and she had been made the subject of several clinics, at which no doubt had been expressed as to the existence of aneurism. Nor is this to be wondered at when one reads Hare's statement: "There was an egg-shaped protrusion in the suprasternal notch, very expansile and bulging with each systole of the heart, and the dilatation extended well up into the vessels." There was great hypertrophy of the heart, a double aortic bruit, and a Corrigan pulse. I had

[1] *New York Medical Record*, 1886, vol. xxix, p. 558.

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repeated opportunities to examine the patient; it was not a case of throbbing of the innominate and the right carotid during ventricular systole, but there was a prominent, dilated tumor to be grasped between the fingers just above the sternal notch. Having had a lesson in a somewhat similar though not so exaggerated a case, I had learned to be very chary in making the diagnosis of aneurism in young persons with aortic insufficiency. At the postmortem it was not a surprise to find the condition had been one of simple dynamic dilatation. The heart was enormously enlarged, there was an extreme degree of insufficiency of the aortic valves, the arch of the *aorta did not admit the index finger, nor the innominate the little finger.* It is important to bear in mind that there may be a permanent fulness of the vessel, so that there is a tumor-like dilatation felt above the sternal notch or the right sternoclavicular articulation. Many of the cases of so-called aortitis and aneurism in young persons following rheumatic fever are of this nature.

2. **Dynamic Dilatation in Neurotic Conditions.**—In hysteria, in neurasthenia, and in Graves' disease the throbbing vessels may lead to diagnosis of aneurism. It is not often that the dilatation and pulsation is of the arch. Bramwell, in his work on *Diseases of the Heart*, p. 723, has reported a remarkable instance in which "pulsation and dulness in the region of the heart were so distinct as to lead Dr. Murray, of Newcastle-on-Tyne, whose diagnostic ability generally, and in aneurism in particular, is well known, to believe that an aneurism of the ascending portion of the arch of the aorta was probably present." Within a few months these physical signs "completely disappeared."

About a year ago the writer was consulted by a clergyman for aneurism of the aorta which had been confirmed by one or two physicians, and he brought an *x*-ray photograph. He was extremely neurotic, had an unusual degree of vascular excitement, throbbing of the subclavians and carotids, and a general jarring of the front of his chest. The *x*-ray photograph suggested a moderate dilatation of the arch. The condition had lasted for a couple of years, and he had become almost incapacitated. A positive assurance that he had not aneurism was followed by an extraordinary lessening of the abnormal pulsation. It is more particularly in the abdominal aorta that the abnormal aortic pulsation leads to error in diagnosis. The subjects of this remarkable pulsation are usually neurotic, sometimes definitely hysterical. They complain of pain in the back and at the occiput, and have the usual symptoms of nervous exhaustion and debility, but the special feature upon which all their feelings centre is the throbbing in the abdomen, which may be so severe as to interfere with their sleeping or even with the taking of food. In extreme cases there are pain, shortness of breath, and even remarkable attacks of hæmatemesis. It is stated that Hippocrates had noticed this pulsation, but to Morgagni we owe the first accurate description. Allan Burns[1] gives a very careful account of the condition, and quotes from Albers, of Bremen, a remarkable instance in which, associated with the throbbing, there was passage of dark blood in the stools. The association of small hemorrhage from the stomach and intestines has been described by Sidney Phillips,[2] but the writer has seen no reported case more remarkable than that of Albers. The girl was excessively neurotic, had faint-

[1] *Observations on Diseases of the Heart, etc.*, 1809.
[2] *British Medical Journal*, 1887, vol. ii.

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ing fits, great palpitation in the abdomen, and an astonishing degree of violent pulsation. She had passage of blood from the bowels, and the diagnosis of aneurism was made, but a Dr. Weinhalt, who was called in, said he doubted if the pulsations proceeded from aneurism, as he had read of similar cases in Morgagni.

The points to be borne in mind in these cases are: (1) That the pulsation occurs in nervous or hysterical women, or in neurotic or hypochondriacal males. In mild forms it is common. (2) The subjective sensations may be pronounced: pain, abdominal distress, nausea, sickness, constipation, and, in some instances, the vomiting of small quantities of blood and the passage of blood in the stools. (3) The degree of visible and palpable pulsation may be extreme. The abdominal aorta is easily palpable and may be grasped in the fingers. It is sometimes tender. No definite tumor is felt. With much anæmia a thrill may be present. A soft systolic bruit may be heard, even without any pressure of the stethoscope. A mistake is not likely to occur if it is remembered that no pulsation, however forcible, no thrill, however intense, no bruit, however loud, singly or together, justify the diagnosis of an aneurism of the abdominal aorta, but *only the presence of a palpable, expansile tumor.*

3. **In Anæmia.**—In extreme anæmia from any cause the bloodvessels throb in a remarkable manner, and may suggest aneurism. This is not often the case in the thoracic aorta and its branches, but in the abdominal aorta it may be extreme. There are conditions, indeed, under which the diagnosis of aneurism seems forced upon us. The writer has often referred to an interesting experience of this kind in a case seen in 1885 with Dr. Whiteside. A large stout man, aged forty-five years, had had for some months dyspepsia and pain in the abdomen. He had become very anæmic, and the day before he was seen he had an increase of the pain. When examined he was sweating, pale, and the large, fat abdomen throbbed in a most extraordinary manner, The shock of the impulse was communicated to the patient's body, was visible everywhere from head to foot, and standing against the foot of the bed one could feel distinctly the jarring impulse communicated to it. On palpation the throbbing was violent with each systole, but it was trifling in comparison with the extent of visible pulsation. There was a loud systolic murmur, but no thrill. That evening he passed a large quantity of blood from the bowels, and though a definite tumor could not be felt, it was thought that the diagnosis of aneurism was certain. The postmortem showed a duodenal ulcer placed directly upon the pancreas. The aorta was normal. In pernicious anæmia in the vessels of the neck and in the subclavians the throbbing may be so violent as to suggest aneurism.

From Other Tumors.—These may be subcutaneous, of the chest wall, or internal. (*a*) *Subcutaneous:* It does not often happen that a tumor beneath the skin on the chest wall is mistaken for aneurism. The suspicious ones which have come under my notice have been associated with necrosis of the sternum and the formation of the cold tuberculous abscess just to the right of it. There may be communicated throbbing, more particularly if the abscess has lasted long and there is periostitis of the posterior part of the sternum directly over the aorta. There may then be a definite jarring which is visible in the tumor. The points of difference are, however, very clear. The abscess tumor is softer, and there is not an expansile, forcible impulse. The shock of the heart sounds is not felt, and there is no murmur,

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More confusing are the rare instances in which the *empyema necessitatis* pulsates. Here, too, the projecting tumor between the ribs has not a strong, heaving, expansile pulsation, but it is a diffuse throb. Then the signs of empyema are usually very clear, and, if in doubt, the needle may be inserted.

The ruptured aneurism of the abdominal aorta may form a very large tumor in the back, or the blood may pass down and form a mass in either iliac fossa, which may be mistaken for abscess or for appendicitis. Nowadays, with the frequency of abdominal operations, the mistake is not uncommonly made. The writer knows of four instances in which under these circumstances operation was performed, thrice for appendicitis, once for supposed abscess. As already mentioned, in some of the very large diffuse aneurisms of the abdominal aorta there may be little or no pulsation. The older authors mention many instances in which aneurism was opened in mistake for abscess. Ambroise Paré mehtions a case of a priest in whom a barber surgeon had opened an aneurismal sac, and the patient bled to death. Morgagni also gives a case.

(*b*) *Of the Chest Wall.*—It does not often happen that a tumor of the chest wall is mistaken for aneurism. Osteosarcoma of the sternum or myeloma of this bone or of the rib may form a tumor to which a jarring impulse is communicated. A vascular osteosarcoma of the sternum may have a very deceptive pulsation of its own, but the writer has not met with any such case and pulsation of a rapidly growing tumor of the rib has been seen, the other circumstances left no doubt as to its nature.

(*c*) *Internal.*—Since the symptoms caused by an aneurism are those of tumor, it is not surprising that difficulties arise in mediastinal and other growths, but these difficulties have been greatly diminished with the aid of the *x*-rays. In two groups of cases error is possible. (1) The *small, solid growth* in the posterior mediastinum connected with the glands or with the œsophagus, which presses upon the windpipe, causing cough and orthopnœa and perhaps paralysis of the left recurrent nerve, gives a clinical picture identical with that of deep-seated aneurism. Nowadays even a very small aneurismal sac may be recognized with the *x*-rays. In a case of mediastinal tumor which gives only symptoms, that is to say, when there is orthopnœa and urgent distress, but nothing to be made out on examination by ordinary means, aneurism is much more likely than new-growth. Occasionally the small tumor of the œsophagus is mistaken for aneurism. The statement is made that an œsophageal bougie, used for purposes of diagnosis, has been thrust into an aneurismal sac, but the writer has not found the record of such a case. The confusing circumstances are those in which there is difficulty in swallowing, attacks of dyspnœa, stridulous cough, and paralysis of the left vocal cord. When the œsophageal tumor is just at the bifurcation of the trachea it may form a small, hard mass involving the recurrent laryngeal and causing great difficulty in diagnosis. In a case of A. L. Scott's at the Pennsylvania Hospital, Philadelphia, in which the tumor occupied this situation, even with the *x*-rays it was not easy to determine the nature of the shadow just to the left of the vertebral column. An important point in the diagnosis of new growth is the age of the patient, which is more likely to be advanced. In the small tumor, whether of glands or gullet, the cervical lymph glands may not be involved.

The voluminous intrathoracic tumor growing from mediastinum, lung, or pleura may offer great difficulty. When situated over the aorta or over

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the heart, particularly to the left of the sternum, the communicated pulsation may be most deceptive, the heaving quite localized, and there is usually a bruit. There is never the strong expansile impulse, felt directly beneath the fingers, and upon this, not upon the extent of visible or palpable impulse, stress should be laid. With venous obstruction and the anterior wall of the chest œdematous and congested, the difficulty may be very great indeed, and the associated features of the case may be more helpful than any other. An enlarged gland above one clavicle or in the axilla, the mode of onset, the age, sex, the history of syphilis, are all important elements. The *x*-ray examination is most helpful in this group, as the outline of the pulsating aorta and heart may be differentiated from the lighter shadow cast by the tumor.

On the other hand, the huge chronic thoracic aneurism may simulate tumor, as the lamination may be so dense that pulsation is absent. In a famous case,[1] Oppolzer diagnosed aneurism and Skoda tumor. The left half of the thorax was flat and there was no pulsation. The patient lived twelve years. The sac filled the greater part of the left chest. Aneurism and sarcoma may occur together, as in a case reported by Virchow in which the two were in direct connection.

From Other Forms of Pulsatile Tumor.—Not every abnormal pulsation indicates an aneurism. It may be well to mention the various forms of pulsatile tumors: (*a*) *Erectile tumors:* The diffuse angioma, in which all the vessels, arteries, capillaries, and veins are involved, forms a red- or violet-looking tumor when the skin itself is involved (which is usually the case), but sometimes it is entirely subcutaneous. The pulsation is diffuse, and a bruit is heard over the tumor. (*b*) Cirsoid aneurism, in which the arteries are chiefly involved; and in the recognition of this form there is rarely any difficulty. (*c*) Ordinary aneurism, true or false. (*d*) The arteriovenous aneurism. (*e*) The very vascular malignant tumors.

The last is the form of pulsating tumor which may be confused with aneurism. Rapidly growing tumors of bone and vascular sarcomata of the abdomen may present an expansile impulse, usually better felt than seen, but occasionally very marked on inspection. The writer remembers only two instances in which the extent and force of the pulsation led to error in diagnosis. One was a man with a large, rapidly growing sarcoma of the upper part of the thigh bone, in which the pulsation was so pronounced that the femoral artery was believed to be involved. The other was an instance of a large sarcoma, probably growing from the retroperitoneal glands, which had a forcible expansile pulsation, and a loud bruit could be heard. In the case of tumors of bone, either in the extremities or in the head, there should rarely be any difficulty; but the pulsating sarcoma in the abdomen is not so easy, particularly when one bears in mind the frequency with which diffuse aneurism of the abdominal aorta has been mistaken for tumor. The important point is the character of the pulsation, which may be diffuse, even expansile, but rarely conveys to the hand that sense of force and strength communicated directly from an aneurism of the aorta or of one of the larger vessels. The bruit over the aneurism is usually louder, but it must be borne in mind that when the sac is very large and filled with masses of coagulum there may be no bruit.

[1] *Deutsch. Arch. f. klin. Med.*, Band xix, p. 623

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Aneurisms Which do Not Pulsate.—There are two conditions in which an aneurism does not pulsate: (1) When a sac is obliterated with laminated fibrin. Sometimes met with in aneurism of the aorta, this is much more frequent in the popliteal and femoral vessels. In the latter regions it is a serious matter, as the leg may be amputated under the belief that the tumor is a sarcoma. Such an instance was seen in Montreal, in which there was a very large mass in the popliteal space which had neither pulsation nor bruit, but proved on dissection after amputation of the leg to be a completely obliterated aneurismal sac. A remarkable case is reported by Hulke[1] and a sequel is given by Baker[2] in his paper "On Aneurisms Which do Not Pulsate." A huge tumor, which proved at postmortem to be an aneurism, occupied the left side of the neck from the trachea to the vertebræ, passed behind the clavicle, filling the axilla, and passed through the superior aperture of the thorax into the left pleural cavity, occupying its upper third and compressing the lung. It sprang from the left subclavian artery. The large aneurism referred to in the previous section did not pulsate. (2) The second condition in which an aneurism may not pulsate is when it ruptures into the neighboring tissues, forming a diffuse tumor. This may occur in the neck, as in the case reported by Hulke and Baker, but it is much more common in the abdomen. As in two cases which the writer has reported, the tumor may be of enormous size and present slight, almost imperceptible pulsation. Sometimes no impulse whatever is to be felt. More particularly is this the case when the tumor extends rapidly in the flanks, forming a large solid mass. If the patient survives, as is sometimes the case, for weeks or months, the clots become firmer and the pulsation may diminish or even disappear entirely. But even very shortly after the rupture the pulsation may be readily overlooked in the intensity of the other symptoms. Many of them present the features of the acute abdomen, and as already mentioned there are a number of recent cases in which the patients have been operated upon for this condition, usually with the diagnosis of appendicitis, without the slightest suspicion on the part of the surgeon that an aneurism was present.

Certain Special Points in Relation to Thoracic Aneurism.—Innominate or arch? The question is important with a view to surgical interference. The innominate is affected in many aneurisms of the arch, either uniformly dilated with it, or the orifice of the vessel is given off in the sac. The high position of the tumor, the presence of pulsation at the sternoclavicular joint without pulsation in the second and third right interspaces, the extension of a definite tumor above the sternal notch, and above all the information to be obtained by the *x*-rays, are the important points. In young persons with aortic insufficiency there may be a prominent tumor above the clavicle, due to dynamic dilatation of the arch and innominate. In the following case a sac of the arch in a peculiar positon led to a mistake in diagnosis: In 1879 there was in the Montreal General Hospital a man, aged thirty-eight years, with a strong pulsation above the right sternoclavicular joint. On palpation the outlines of the tumor could be felt, with a smooth, rounded border just above and behind the joint. Vigorous lateral pulsation was felt with one finger in the sternal notch and the other at the outer border

[1] *Clinical Society's Transactions*, 1878, vol. xi, p. 123.
[2] *St. Bartholomew's Reports*, 1879, vol. xv, p. 75.

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of the sternocleidomastoid muscle. There was flatness behind the inner end of the right clavicle. A loud, systolic murmur was heard, but he had no aortic insufficiency. There was slight paralysis of the right cord. The question arose as to the possibility of cure by distal ligature, as the aneurism was thought to be of the innominate. He refused operation, and died of pneumonia about four months later. At the postmortem a dilated aortic arch was found, and just before the innominate was given off there was a small aneurism the size of a walnut, conical in shape, which passed up by the side of this vessel, occupying a position immediately behind the sternoclavicular articulation.

The X-rays.—With a good apparatus in the hands of an expert the results are of extraordinary value. For the technical details of the examination the reader is referred to special monographs. There is rarely difficulty in the diagnosis of the saccular aneurism, as the shadow pulsates and the rounded mass is readily differentiated. F. H. Baetjer, who had a very large experience with aneurism at the Johns Hopkins Hospital, classifies the positions as follows:

1. "Aneurism of the ascending portion of the aorta usually casts a shadow more to the right than to the left of the sternum, above the heart, and by localization would be found to be nearer the anterior than the posterior wall of the chest."

2. "Aneurism of the arch casts a shadow slightly to the left of the sternum, and this shadow extends well up into the neck, and by localization would be found nearer the anterior chest wall."

3. "Aneurism of the descending arch of the aorta casts a shadow to the left of the sternum, and by localization would be found nearer the posterior than the anterior chest wall."

In the diffuse aneurism with the arch uniformly dilated a broad shadow extends along the sternum on both sides, and pulsation of the shadow may be seen and the shadow persists between pulsations. In the simple dynamic dilatation of the aorta, pulsation of the shadow is visible, but between the pulsations the shadow disappears, as the aorta contracts and its shadow lies within that cast by the sternum and the spine. In large aneurisms the depression of the heart and its somewhat transverse position are usually well seen. It is particularly in the group of aneurisms without physical signs that the *x*-ray examination is of the greatest possible value. We had at the Johns Hopkins Hospital a most interesting series of such cases, many of which have been reported by Baetjer. One is greatly impressed with the accurate localization of the tumor in some of these latent cases. A woman, aged twenty-three years, was admitted cyanosed and with urgent dyspnœa. There was evidently tracheal compression. After she was relieved by venesection a most careful examination of the chest could detect but one physical sign—less air entered the lower lobe of the left lung than the corresponding lobe of the right lung. The *x*-ray examination showed a small aneurism of the transverse arch; the position corresponded accurately with that as determined at the postmortem. Several of the latent cases presented only persistent pain. In skilful hands there is rarely much confusion between aneurism and tumor. Williams, the pioneer in radioscopic work in internal medicine in America, very fully sums up the position in the following words: "To make a definite diagnosis of aneurism by the usual physical examination we may be obliged to wait for the development of marked signs, and this

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PLATE I

Skiagram of an Aneurism of the Thoracic Aorta.

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delays treatment. On the other hand, if the physician begins treatment because the signs are suspicious, he runs the risk of subjecting his patient to unnecessary regimen. The advantages of *x*-ray examination when compared with the usual physical examination are evident. A definite diagnosis can be made in most cases before there are physical signs. Treatment can, therefore, be begun at an earlier and more hopeful stage, can be planned more intelligently as the knowledge of the position and extent of the aneurism is more accurate, and its results can be better estimated because we can more accurately measure any change in size."

PROGNOSIS OF ANEURISM.

In aneurism of the aorta itself the outlook is always grave, and yet a number of cases recover. The mode of cure has already been spoken of. Canby Robinson, in an examination of the specimens in the Philadelphia Museum, was able to find many cases of spontaneous healing. In the great majority the aneurism had been latent. Lebert estimated that the period of the evolution of an aneurism was from six months to four years. In a great majority of all cases the fatal result occurs within two years from the onset of the symptoms. The most favorable is the saccular form projecting anteriorly or to the right, but it is not always easy to determine the exact shape, although now with the *x*-rays one can often get a very good idea of the form. Once an aortic aneurism is healed, the individual may live for many years. Under Dissecting Aneurism the case of a soldier who was invalided for aneurism after the Crimean War, in 1855, and who lived until 1881, was mentioned. Among favoring elements in the prognosis are: (1) Position and form of the sac. Moderate-sized, saccular aneurisms of the ascending arch of the descending part and of the abdominal aorta are more frequently seen obliterated than those springing from the transverse arch. (2) Early diagnosis and treatment. In the case of a young man who has had syphilis, specific treatment thoroughly carried out, in combination with absolute rest, gives at least a chance of cure. (3) In a few instances the sac projecting anteriorly has been permanently occluded as a result of operation. The San Francisco case operated upon by Rosenstern lived for many years. Even after a sac has perforated the chest wall, life may be prolonged. Jamieson reported the case of a man aged thirty-two years, who lived and worked for twelve years with an aneurism projecting through the chest wall. There are deceptive features in thoracic aneurism which must be taken into account in the prognosis. The pulsating tumor may diminish, may even disappear, and yet the sac may increase in another direction. In a case of this kind, which was seen with George Ross, of Montreal, the patient had been most faithful in carrying out a strict Tufnell treatment, and had taken potassium iodide in very large doses. The pulsation anteriorly had lessened remarkably, and it was thought that surely the aneurism was healing, but he died suddenly of rupture into the pleura, into which, it was found at postmortem, the sac had extended.

Death takes place usually from the rupture of the sac, sometimes from sudden paralysis of the heart, rarely from the effects of pressure or from gradual asthenia.

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TREATMENT OF ANEURISM.

Necessarily in great part symptomatic, only in a few cases is a cure effected. In a case of thoracic or abdominal aneurism seen early the following plan of treatment may be carried out:

1. *Rest.*—By diminishing the vigor of the heart's action, and possibly by diminishing the volume of the sac, there is often an extraordinary relief to the cough, the shortness of breath, and the pain. The rest should be complete, the patient remaining for from six to twelve weeks in the recumbent posture and making as few movements as possible. It is not an easy treatment to carry out. If the aneurism is large and has already eroded the chest wall, it is hardly worth while to insist upon prolonged rest. Between the recumbent posture and the erect with exercise the reduction of the number of pulsations per minute in the sac may be from twenty-five to thirty, so that in the course of the day there is a considerable saving of the strain upon its walls.

2. *Diet.*—The intake of solids and liquids may be reduced to a minimum. Tufnell's diet is as follows: "For breakfast, two ounces of bread and butter and two ounces of milk or tea; dinner, three ounces of mutton, three ounces of potatoes or bread, and four ounces of claret; supper, two ounces of bread and butter and two ounces of tea; total *per diem*, ten ounces of solid food and eight ounces of fluid, and no more." Only in early cases is it worth while to put the patient to the serious inconvenience of this diet.

3. To aid in the reduction of the blood pressure, and to increase the tendency to coagulation in the sac, small bleedings may be practised, five or six at intervals of a week, taking six to ten ounces of blood. This triple combination of rest, low diet, and bleeding is the Valsalva method, which was used with success by Albertini and other Italian physicians in the eighteenth century. Morgagni gives it succinctly: "When as much blood as was requisite was withdrawn (by repeated small bleedings), he (Valsalva) ordered a progressive diminution of food and drink until the quantity was reduced to a determined weight of aliment and water. Having so enfeebled the patient that he could scarcely raise his hand from bed, on which he was ordered to lie from the beginning, the quantity of aliment was cautiously increased." Morgagni remarks: "There are many persons to whom Valsalva's method of cure may appear more intolerable than the aneurism itself, especially at the only time when any treatment could avail. The inconvenience of the disease at that period is but slight and the danger is not imminent, etc."

4. *Iodide of Potassium.*—The value of this drug in aortic aneurism is undoubted. Formerly the favorable results were attributed to condensation of the sac by its action on the fibrous tissues and to the promotion of coagulation. A more rational view is that the luetic mesarteritis is directly influenced by it. It is remarkable the promptness with which the pain is relieved in the syphilitic cases. Formerly we gave enormous doses, up to 200 and more grains three times a day, but of late years the writer has found that moderate doses are just as effective, and it is rarely necessary to give more than 25 to 30 grains (1.5 to 2 gm.) three times a day. When the syphilis has been recent mercurials may be given as well.

5. *Measures to Allay Pain.*—The iodide of potassium often gives relief. Local applications—belladonna plasters, an ice-bag, a hot poultice, or a hot-water bottle—are helpful, but in the majority of cases, where the pain is due

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to pressure, morphine must be given. And in such a desperate malady it is well to give it early and freely.

6. Additional measures employed *to increase the coagulation of the blood.* To assist the low diet and rest and iodide of potassium in promoting the coagulability of the blood, calcium lactate may be given in from 15 to 20 grains (1 to 1.3 gm.) doses three times a day. Gelatin subcutaneously injected, 200 to 250 cc. of a 2 per cent. solution, was introduced by Lancereaux. The writer gave it a very thorough trial for several years, and the cases from his clinic have been reported by Futcher. In one or two instances it seemed to diminish the pain and lessen the size of the sac; but we did not get in any case the brilliant results which the distinguished author of this plan of treatment reports. Of 126 collected cases from the literature, benefit followed in 58 (v. Bottenstern).

Not in every case of thoracic or abdominal aneurism should a *cure* be attempted. A majority of the patients come under observation at a period when symptomatic treatment is alone possible. In what class of cases may a cure be expected? In the young syphilitic subject under thirty, in whom the diagnosis is made early, in cases in which the fluoroscope shows a small and sacculated aneurism, and in elderly persons, in whom, as postmortem experience teaches, the sac may spontaneously heal. When the sac is large, or if the fluoroscope shows a diffuse dilatation of the arch, it is best to allow the patient to continue his occupation, unless it is too arduous, and treat the symptoms as they arise.

What is to be done to relieve the frightful pressure dyspnœa? Patients are not infrequently brought to hospital cyanosed, gasping for breath and literally choking to death. As already stated, it is not always easy at first to make a diagnosis, but it is well to remember that in 9 out of 10 of such cases in adult males aneurism is the cause. Venesection from one or both arms to 25 or 30 ounces may give prompt relief. The removal of much smaller amounts may be effectual. It may be repeated several times in the course of a week. There are very few conditions in which free bleeding is so helpful. Morphine hypodermically should be given, unless there is an extreme degree of pulmonary infiltration, as shown by fine bubbling rales. In any case, if the patient is *in extremis* and suffering, it should be given. In the paroxysmal dyspnœa suggesting spasm of the larynx, due to irritation of the recurrent laryngeal nerves, the inhalation of chloroform may be tried; even if not immediately relieved, the comfort to the sufferer is very great. Should tracheotomy ever be performed in these cases? Theoretically, of course, with an aneurism or a tumor garroting the trachea at the bifurcation, it is useless, and yet it is often impossible to resist in the case of a poor fellow admitted choking and in a dying state. The writer has seen it done in a good many cases, never with permanent benefit, occasionally with temporary relief. In one case the woman's suffering was so frightful that after a preliminary tracheotomy Dr. Halsted attempted to reach the seat of compression by resecting the upper portion of the sternum, on the chance of giving freedom in this way and possibly of placing one of his rings about the aorta above the sac, the position of which could be accurately defined with the fluoroscope. The patient died on the table in a paroxysm. In a case at the West London Hospital, under Seymour Taylor, tracheotomy gave immediate relief.

Surgical Treatment of Internal Aneurism.—*Ligation* of the aorta has been done ten or twelve times for aneurism of the abdominal aorta, always

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with fatal result. *Digital compression* has been tried in many cases. William Murray, of Newcastle-on-Tyne, cured a man aged twenty-six years, who had a pulsating tumor to the left of and above the umbilicus. Between the sac and the free border of the rib there was room enough to permit one part of a tourniquet to press on the spine and control the pulsation. The patient was put under chloroform for two hours, during which time the pulsation was arrested. On removal of the pressure there was no effect. Three days later the pressure was again applied under anæsthesia of five hours' duration. In the last hour the pulsation was no longer evident when the tourniquet was released, the extremities were cold, and the femorals could not be felt. The patient got perfectly well and lived six years, when another aneurism occurred at the cœliac axis.[1] A number of successful cases have been reported. When by digital compressions or a tourniquet the pulsation in the sac may be obliterated, this is the safest method. But it is not always satisfactory, and death has followed from peritonitis, obstruction of the bowels, and reduction of the pancreas to a pulp.

Insertion of Foreign Bodies in the Sac.—In 1864, C. H. Moore, of the Middlesex Hospital, attempted the cure of aneurism by the introduction of wire into the sac, believing that by it coagulation of the blood would be favored. He put 78 feet of fine wire into the sac of a thoracic aneurism. Death occurred on the fifth day. Many other substances have been used, catgut, horsehair, Florence silk, etc. It has not been a very successful method. In October, 1900, Hunner collected 14 cases, 8 of thoracic aneurism, all fatal; 6 of abdominal aneurism, with 3 recoveries.

Electrolysis.—Corradi recommended the passage of an electrical current through the wire inserted into the sac, and this Moore-Corradi method is the one most frequently used.

In the hands of Finney and Hunner at the Johns Hopkins Hospital the technique has been much improved,[2] and the operation is one that may be performed with safety in suitable cases. Of 23 cases treated in this way, 17 thoracic and 6 abdominal, 4 were cured. Rosenstern's patient was alive seventeen years after the operation. Three cases were improved. In 10 cases death was probably hastened. Of my series of cases of aneurism of the abdominal artery, 7 were treated by the Moore-Corradi method, 2 were improved, and 1 was alive three and a half years after the operation. The sacculated tumor with small orifice is best adapted for this, and with the improved facility afforded by the *x*-rays in determining the position and shape of the aneurism the chief difficulty will be overcome in the selection of suitable cases.

Needling the Sac.—Macewen introduced the practice of needling the inner lining of the aneurism with a view of promoting thrombus formation. It has been successful in a few cases. The practice of injecting irritating liquids into the sac—iodine, tannin, perchloride of iron—has been given up.

For the statistics of the surgical treatment of the important recent series of cases of arterio-venous aneurism the reader is referred to W. F. Stephenson's *Report on the Surgical Cases in the South African War*, London, 1905, p. 223, and to the paper by Saigo in the *Deutsche Zeitschrift f. Chirurgie*, Bd. xxxv, on traumatic aneurism in the recent Japanese-Russian War.

[1] *Medico-Chirurgical Society's Transactions*, 1864. *Inductive Method in Medicine*, Murray, 1891, p. 120.

[2] *Johns Hopkins Bulletin*, 1900, vol. xi, p. 263.

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CHAPTER XII.

THROMBOSIS, EMBOLISM, AND PHLEBITIS.

By GEORGE BLUMER, M.D.

THROMBOSIS.[1]

The old definition of thrombosis as a "clotting of the blood in the heart or vessels during life" is no longer tenable, for while there is little doubt that the process of coagulation plays an important part in the formation of many thrombi, it is now clear that in a certain proportion of instances, and that perhaps not a very small one, agglutination is the predominant process. Indeed some writers, L. Loeb, for example, suggest that agglutination plays a part in all thrombus formation. The process is better defined, therefore, as Welch points out, as "the formation of a solid mass or plug in the living heart or vessels from constituents of the blood." The term thrombus is applied to the plug so formed.

Etiology.—It seems certain that chemical changes in the blood play an important part in the causation of thrombosis, but so long as our knowledge of the coagulation of the blood under normal conditions remains as incomplete as it is at present, it cannot be expected that the exciting factors governing thrombosis associated with abnormal clotting will be very well known. According to the conception now most widely held, coagulation is a complex process involving the formation of fibrin as the result of the action of a ferment, thrombokinase, upon thrombogen, the process occurring only in the presence of lime salts. Normally thrombogen is found in the blood and lymph as prothrombogen, and is not set free as thrombogen until these fluids escape from the vessels and come into contact with the tissues. Thrombokinase is found in a variety of tissues, especially muscle and certain glands, is present in the walls of the bloodvessels, and is possibly set free by the destruction of red corpuscles. If we conceive coagulative processes to be of vital importance in the process of thrombosis we can imagine a variety of conditions which might favor their intravascular occurrence: the entrance of the thrombokinase into the circulation, the formation of thrombogen in the circulating blood, an increase of the lime salts in the plasma, or various combinations of these three conditions, suggest themselves. Such conceptions are almost purely theoretical, but in some instances they seem to fit in fairly well with the known facts. Knowing that the walls of the vessels contain thrombokinase, it can be imagined that an injury of a mechanical, bacterial, or toxic nature, which would expose the vessel wall to the circu-

[1] Most of the literature on thrombosis may be found in the articles of Welch (Allbutt's *System of Medicine*), Forel (*Ergebnisse der allg. Path. Jahr.*, ix, Abt. 1, 1903), and Haward (*Phlebitis and Thrombosis*, London: Baillière, Tindall, and Cox, 1906). The foot-notes in the text usually refer to articles dealing with special points or containing many important references.

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lating blood, might produce thrombosis. If, as some suppose, the destruction of red blood corpuscles sets free fibrin ferment, the predisposition to thrombosis which accompanies certain anæmic, cachectic, and infectious states is elucidated. The factors governing thrombogen formation are little known; it is conceivable that errors in metabolism or the circulation of toxins in the blood might lead to the transformation of prothrombogen into thrombogen within the vessels, but this in the absence of thrombokinase would not lead to coagulation. The presence of an excess of calcium salts in the blood serum would likewise, of itself, be insufficient to cause thrombosis, but increase either in these salts or in thrombogen would doubtless render the probabilities in favor of thrombosis much greater than under normal circumstances. Whether a part is played in thrombosis by individual peculiarities in body chemistry is not definitely known, but in any consideration of the etiology of the condition the personal element should not be forgotten. Under apparently identical conditions one individual develops thrombosis while another fails to do so. While, so far as we know, there is no convincing evidence of a definite family tendency to thrombosis, such as is comparable to the tendency to bleeding in hæmophilia, it is possible that individual peculiarities in the production of thrombogen or thrombokinase may play a part. Sahli has brought forward a good deal of evidence to show that in hæmophilia there is a lack of thrombokinase in the vessel walls; it is possible that in certain individuals the opposite condition prevails, so that in the presence of certain predisposing factors thrombosis occurs. There are instances on record of a family tendency to phlebitis with thrombosis, but this factor does not apparently play a part in all instances of thrombosis.

The importance of agglutination as a factor in thrombus formation has been strongly emphasized by the work of recent years. That agglutination played a part in the formation of some thrombi was suggested by Hueter in 1873, and later emphasized by v. Recklinghausen and by Welch. The more recent studies of Flexner, Pearce and Winne, and others tend to show that thrombi due to agglutination pure and simple, and lacking in evidence of the action of coagulation, are much more common than was formerly thought to be the case. One class of thrombi especially, the so-called hyaline thrombi, must be definitely regarded as, in many instances, metamorphosed plugs of agglutinated red corpuscles. Flexner suggests that the so-called "fibrin-ferment thrombi" belong in the same class. These hyaline thrombi are most common in the smaller vessels in connection with infectious diseases, but in some instances larger thrombi, such as those of the femoral vein and of the heart cavities, have been shown to be due to agglutination and not to coagulation. The agglutination is believed to be usually due to the formation of hæmagglutinins by bacteria. It has, in fact, been shown experimentally that a variety of bacteria possess the power of producing hæmagglutinins, some more strongly than others. In human and animal pathology, agglutination thrombi have been found in connection with typhoid fever, lobar pneumonia, plague, pyococcal infections, experimental diphtheria, hog cholera, and other diseases of bacterial origin. Intoxications, both with bacterial and vegetable poisons, are also capable of causing agglutination. Agglutination thrombi have been noted in association with poisoning by ricin, and with diphtheria, tetanus, and streptococcus toxins, and similar lesions have been observed in eclampsia and carbolic acid poisoning. The

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various toxic processes of obscure origin associated with blood destruction are also provocative of agglutination thrombosis, as the destruction of red corpuscles leads to the formation of hæmagglutinins. This suggests that the thrombosis seen in certain forms of anæmia of toxic origin is probably of agglutinative rather than coagulative origin.

That morphological changes in the blood have any marked bearing on thrombosis is, to say the least, dubious. The prominent part played by blood platelets in the process of thrombus formation has led some observers to the conclusion that increase in these elements is a cause of thrombosis. An inquiry into the relation of the platelets to the various diseases in which thrombosis is common does not bear out this view in a convincing manner. In some diseases commonly associated with thrombosis, as chlorosis, the platelets are increased; in fevers, too, while the platelets are diminished during the early stages, they are sometimes markedly increased during convalescence,[1] at the time when thrombosis is most likely to occur. Still, definite platelet counts made in patients with thrombosis have not always shown an increase in their number; in some cases, indeed, a decrease has been noted. The work of Pratt and others has shown that so far as coagulation thrombi are concerned there is, judging from normal coagulation, little likelihood that the thrombus formation is intimately associated with increase in platelets. Just what relation such an increase may bear to agglutination thrombi must, we think, be left an open question. We can but conclude that, although increase in the platelets may play a part in some instances, it is not a necessary factor in all cases.

Theoretical considerations aside, we are acquainted with certain predisposing factors which are quite constantly associated with thrombosis, and these concern mechanical rather than biochemical conditions affecting the circulation. The most important of these factors are slowing or irregularity of the circulation, and lesions of the walls of the heart or vessels which impair their smoothness and integrity. Of itself, slowing of the blood current is incapable of causing thrombosis, numerous experiments, especially those of Baumgarten and Rizor, having shown that a column of blood contained in a segment of a vessel included between two ligatures may remain fluid for weeks, provided that the ligatures be applied under aseptic conditions, and with sufficient care to avoid injuring the vessel wall. That decreased velocity of the blood stream plays an important part in thrombosis in human beings is shown by the fact that the points of predilection for thrombosis are those parts of the circulatory apparatus through which the blood flow is slowest. Aside from mere slowing of the blood current, stress has been laid by v. Recklinghausen on the occurrence of thrombi in situations where the blood stream has a whirling or eddying motion. Such whirls and eddies are found especially in certain parts of the cavities of the heart, but are also present where there are obstructions to the blood current from the valves of the veins or pathological processes, and in those situations where the blood column is suddenly projected from a vessel of small caliber into a larger one.

The part played in thrombosis by the condition of the lining membrane of the heart and bloodvessels has been recognized from a date early in the history of the study of the condition. Experiment has shown that the introduction into the blood stream of sterile smooth objects, such as glass balls,

[1] Tschistowitz, *Folia Hæmatologica*, 1907, vol. iv. No. 3.

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does not lead to thrombus formation, while, on the other hand, rough foreign bodies quickly cause thrombosis. The influence of the purely physical quality of smoothness is also illustrated by the experiments of Freund, who showed that blood carefully introduced into oiled receptacles remained fluid for some time. Aside from the physical effects of roughening of the heart or vessel wall chemical factors also play a part in predisposing to thrombosis. This has long been recognized, and was explained by Zenker on the ground that destruction of the endothelium set free fibrin ferment. Recent studies suggest that the exposure of the vessel wall, which is known to contain fibrin ferment, may be a more important factor. There is no doubt that the character of the lesion is also of moment, the tendency to thrombosis being much greater in connection with septic injuries than it is when the vascular lesion is aseptic or due to degenerative lesions.

The relation of infection to thrombosis has, of late years, been strongly emphasized. Many thrombi have been investigated bacteriologically with the result that bacteria have been found frequently, not only in thrombi associated with definite infectious processes, but also in the so-called marantic thrombi which occur in chronic debilitating diseases. The subject has been attacked experimentally by Jakowski, Talke, and others. At the present time there is no question that the commonly accepted view regarding definite infectious thrombo-angeitis is that the vascular lesion is the primary one, the thrombosis being secondary. This view is, as a rule, borne out by the histological changes and by experimental work, although it cannot be denied that in some instances in which bacteria have been definitely associated with thrombi the vascular lesions have been slight or even lacking. There is still disagreement as to the actual modus operandi of bacterial infection in the production of thrombosis. Possibly the changes which lead to thrombus formation are not the same in all instances. Injury to the vessel wall, particularly destruction of the endothelium, may be produced by either bacteria or toxins, and, as previously mentioned, could well cause thrombosis on account of the mechanical effect and the setting free of thrombokinase. In cases of definite thrombo-angeitis it is certain that the thrombosis is mainly produced through the changes in the vessel wall, although even in these cases there is disagreement as to whether the bacteria or their toxins cause the thrombus formation. Talke claims that bacteria are not present in such thrombi during the early stages, and that the thrombus formation is of toxic origin. In infected thrombi which are not associated with gross changes in the vessel walls the role of bacteria is uncertain. Some have claimed that the bacterial toxins directly cause thrombosis; others believe that they act indirectly by modifying some of the factors which govern coagulation or agglutination. That certain bacteria possess definite power to cause both coagulation and agglutination has already been mentioned. In a general way it would perhaps be fair to say that although it is certain that infection plays a very important role in thrombosis, the importance of bacteria as a direct cause of thrombosis has been somewhat exaggerated.

Trauma, aside from injuries associated with infection, plays but a small part in the etiology of thrombosis. There are to be found in the literature[1] occasional instances in which a tear of the inner coats of an artery has been followed by thrombosis. This accident has been noted most frequently in

[1] Stern, *Traumatische Entstehung innerer Krankheiten*, Jena, 1907.

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the popliteal artery, and has usually resulted in gangrene of the foot. There are a few instances on record of thrombosis of the larger arteries, such as the iliacs, after abdominal contusion, but their occurrence is uncommon. Wilke has reported one rather unconvincing instance in which thrombosis of the portal vein seemed to be dependent upon an injury of a jarring nature. There are undoubted instances, such as that reported by Bohm, in which a thrombus of traumatic origin occurring in the superficial veins has extended to main trunks, and caused the death of the individual.

Etiological Relationship of Various Diseases to Thrombosis.—The relation of thrombosis to various diseases, so far as the fatal cases are concerned, is shown by the figures of Mannaberg and Haward.[1] Mannaberg's statistics cover 1800 autopsies performed in the Pathological Institute, in Vienna. Of these 1800 patients, 96 (or 6 per cent.) showed the presence of thrombosis. In 39 instances it was associated with infectious diseases; in 30 with cardiac and vascular diseases; in 19 with new-growths; in 6 with marasmus, and in 1 each with chlorosis and nephritis. Haward's table covering 80 instances of thrombosis showed an association with middle-ear disease in 14 cases, with cancer in 12 cases, with varix in 6 cases, with appendicitis in 4 cases, with gastric ulcer, ovariotomy, and abscess of the liver each 3 cases, and with puerperal sepsis, metritis, intestinal ulcer, heart disease, and pleurisy each 2 cases. It is necessary to call attention to the fact that these figures refer only to fatal cases, and are not, therefore, the true index of the frequency of thrombosis, inasmuch as in certain diseases with which thrombosis is commonly associated death is unusual as a result of this complication. Certain disease associations of thrombosis are so important that it is necessary to consider them somewhat at length.

Thrombosis in Typhoid Fever.—Cardiac thrombi, apart from those occurring in connection with endocarditis, are uncommon in typhoid fever. In rare instances, usually in individuals with great feebleness of the circulation, thrombi may form in the cavities of the heart, more especially in the auricular appendages and the apices of the ventricles, as they do in other conditions associated with cardiac weakness.

Arterial thrombosis is also very uncommon in typhoid fever. Thayer[2] records 5 cases of arterio-thrombosis among 1458 cases of typhoid fever. In 3 the peripheral arteries were involved; in the other 2 the cerebral arteries. In 2 of the patients the evidence of complete plugging of the vessels was doubtful. Eichorst states that of 23 cases of peripheral gangrene following typhoid fever collected by Ferrand, 22 involved the lower extremities. Eichorst's own series[3] of 38 collected cases of peripheral arterio-thrombosis with gangrene occurring in typhoid fever shows a similar involvement of the legs and thighs. Of the 38 cases 3 involved the upper extremity, 35 the lower. Of the latter number, the exact location of the lesion was stated in 24, of which 10 involved the left leg, 10 the right leg, and 4 both legs. In cases with gangrene, and this usually occurs, the leg and part of the thigh are most commonly involved, although occasionally the foot only or single toes or fingers are affected. In striking contrast to the venous thrombosis occurring in typhoid fever is the equal frequency of involvement of the two

[1] Haward, *Phlebitis and Thrombosis*, London, 1906.
[2] *Johns Hopkins Hospital Bulletin*, October, 1904, vol. xv.
[3] *Deut. Arch. f. klin. Med.*, 1901, vol. lxx.

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sides. There are, besides these cases with gangrene, others in which there was little doubt of the existence of arterio-thrombosis, perhaps only partial, however, and in whom recovery took place. Some of Thayer's patients gave this history. Thrombosis of other than peripheral arteries in typhoid fever is probably more common than postmortem records would indicate. It would seem as though the branches of the cerebral arteries, and especially of the middle cerebral, were unusually liable to this complication, for hemiplegia and aphasia are not excessively uncommon as complications of the disease. Other arteries, such as the pulmonary or mesenteric, are also occasionally involved. The complication usually occurs during the febrile period of the disease, although this is not invariably the case. It is difficult to judge from clinical observation alone how frequently the arterial lesions in these patients are embolic rather than thrombotic. Eichorst's series of cases, in many of which examination of the amputated limbs was made, indicates that thrombosis is probably much more common than embolism. The cause of the complication is generally held to be local infection of the artery. While there is some evidence in favor of this, both experimental and histological, the amount of bacteriological work still remains too small, as Welch suggested in 1900, to form a basis for a definite opinion.

Venous thrombosis is very much more common in typhoid fever than cardiac or arterial thrombosis. It occurs, according to Thayer's figures, in a little over 2.5 per cent. of the cases. Of Thayer's 42 cases, which occurred among 1458 patients, 40 involved the veins of the lower extremity, and 26 of these were on the left side. The femoral vein was the one most commonly involved, 50 per cent. of the thromboses occurring in it. The popliteal, iliac, and calf veins were involved only one-fourth as frequently as the femoral. The internal saphenous was occasionally thrombosed.

Thrombosis in Pneumonia.—As in typhoid fever, so in pneumonia, cardiac thrombosis, aside from the thrombus formation associated with the not infrequently complicating endocarditis, is a rarity. There are many accounts of cardiac thrombi in this disease in the older literature, but, as Welch has pointed out, most of these are not authentic, and are due to the fact that in this disease unusually firm postmortem clots are formed which are mistaken by the uninitiated for antemortem thrombi.

Peripheral arterio-thrombosis is unusual in pneumonia, and a good many of the reported instances impress one as being more probably due to embolism than to thrombosis. In some instances, however, operation or autopsy has proven that the lesion was thrombosis, as in the cases of Cruveilhier, Benedikt, and Zuppinger. Some of the cases occurred in very old people and were associated with extreme feebleness of the circulation. Most of the reported cases involved the lower extremities, although in arterio-thrombosis accompanying pneumonia the lower limbs are not involved so constantly as they are in venous thrombosis in this disease. Women seem more subject to the complication than men, although the reported cases are too few to judge of this with accuracy.

Venous thrombosis is a rare condition in lobar pneumonia, a rather surprising matter, as Steiner points out, when we consider the richness of the blood in fibrin in this disease. Up to 1902, Steiner[1] was able to collect but 38 cases of peripheral venous thrombosis in connection with this disease.

[1] *Johns Hopkins Hospital Bulletin*, June, 1902.

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Thrombosis of internal vessels, if we except the constant thrombosis of the small pulmonary vessels in the involved lung, is rarer still, though Lipman-Wulf has recorded an instance of thrombosis of the vena cava, and occasionally the large branches of the pulmonary artery are involved. The condition occurs as a sequel rather than a complication of pneumonia, about seven-eighths of the cases being recorded as occurring during convalescence. As in most forms of venous thrombosis, the lower extremities are involved much more frequently than the upper, in fact almost exclusively so in this disease, if one can judge from the small number of recorded cases. The femoral vein is most frequently involved either alone or with the internal saphenous. The popliteal and iliacs are occasionally the seat of thrombosis. The left side, as usual, is more frequently attacked than the right. Death occurred in 9 of the 34 cases collected by Steiner, and in the majority of the patients who came to autopsy it was found to be due to pulmonary embolism.

Thrombosis in Influenza.—As would be expected in a disease in which marked heart weakness is a not infrequent feature, cardiac thrombi of a marantic nature have occasionally been reported in influenza, and a few instances of globular thrombi are on record. Thrombosis as a part of a valvular endocarditis has been reported a number of times in recent years, and bacilli having the morphology of influenza bacilli have been isolated from the valvular vegetations by Austin and others. Horder has cultivated the bacilli from the blood during life.

Arterial thrombosis is more common in influenza than in most of the infectious diseases. It was first noted late in the eighteenth century, and a fairly large number of instances have been reported since the outbreak beginning in 1889. In the German epidemic of 1894 there were only 2 cases of arterial thrombosis reported among 38,432 patients. In a collective investigation made in Germany after the pandemic of 1889–90, 8 cases were reported. Eichorst was able to collect 19 cases of influenza with gangrene of the extremities up to 1901, and 18 of these were in all probability due to arterial thrombosis. The lower extremities were attacked in 16 out of the 18 patients, a single toe in 1 instance, both legs twice, and one leg thirteen times. The right leg was more often attacked than the left, judging from Eichorst's figures. According to Welch, the popliteal artery is most frequently involved, next the femoral, and less frequently the iliacs, axillary, and brachial. In 5 out of the 8 cases collected by the German committee the popliteal artery was affected. Of arteries other than those in the periphery, the cerebral are most frequently involved. Thrombi in the pulmonary arteries have been noted by Lasker and Flexner, the latter having isolated influenza bacilli from the thrombus in his case.

Venous thrombosis is of relatively frequent occurrence in influenza, and may occur either during the attack or late in convalescence. The German committee collected 25 cases following the pandemic of 1889–90. The influenzal thrombosis resembles that of other infectious diseases in that the veins of the lower extremities are usually attacked, although the brachial and axillary veins are more frequently the seat of thrombosis in this disease than in most infectious diseases. The veins most frequently involved are the femorals and the veins of the calf. The complication, while occurring most frequently in severe cases, is by no means unknown in the lighter forms of the disease. Leichtenstern thinks that venous thrombosis in influenza

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is more apt to lead to gangrene than is usually the case with plugging of the veins, probably as a result of the great suddenness with which total blocking of the vessels occurs. This may be the case, but the number of venous thromboses with gangrene which are on record is still very small, and the unusual number of cases of gangrene may be due to coincidence or to the fact that most of them occur in people past middle life in whom arterial changes may also be present. In Johannsen's patient there was, in fact, arteriosclerosis as well as venous thrombosis.

The origin of the thrombosis in influenza is a matter of dispute. Some cases are in all probability infectious, and due either to the action of the influenza bacillus or some secondary invader upon the vessel walls. In many patients, especially those with arterial thrombosis, preëxisting arteriosclerosis and the debilitating effect of the disease on the circulation seemed to be powerful predisposing causes. Changes in the blood itself have been suggested, as this is one of the diseases in which there may be a marked increase in blood platelets, but, as stated elsewhere, the evidence that this factor is of importance is not conclusive.

Thrombosis in Appendicitis.—The frequency with which thrombosis occurs in appendicitis has been widely commented upon in recent years. Arterial thrombosis is very rare, but cases with gangrene have been recorded by King and von Leyden. Venous thrombosis is relatively common. Haward's figures from the London hospitals show that it occurred thirty-four times in 3774 patients with appendicitis. The figures from Halstead's clinic, 4 thromboses in 131 patients, give a much higher percentage, but, on account of the small number of cases, are less likely to be accurate. In the vast majority of instances of venous thrombosis accompanying appendicitis the femoral vein was involved, usually on one side only, occasionally on both. The iliac vein and the calf veins are at times the seat of the thrombus formation, and Lockwood has seen 2 instances of thrombosis of the mesenteric veins. In many of the cases in which the seat of the thrombosis is indicated it has been on the left side, although the figures of some authors indicate an almost equal frequency on the right side. Pulmonary embolism occurred in Haward's series in a little less than one-eighth of the cases with thrombosis. As Welch points out, these thrombi are analogous to puerperal thrombi, inasmuch as in both diseases septic thrombi in the immediate neighborhood of the diseased organ are common. As in other thrombi associated with infectious processes, the cause of the lesion is probably in many instances the metastasis of infectious material with local involvement of the vessel wall. The fact that the primary lesion is on the right side and the thrombosis rather more likely to occur on the left makes a direct extension from the veins about the appendix unlikely. Possibly prostration and weakened circulation may play a part in some cases as Mynter suggests, but inasmuch as the complication occurs in chronic as well as in acute attacks and in patients operated on between attacks, this cannot always be a factor.

Postoperative Thrombosis.—Attention may here be briefly directed to postoperative thrombosis, although strictly speaking the subject is a surgical one. The figures from Kümmel's clinic covering 1140 laparotomies show that thrombosis occurred 53 times, or in a little over 4½ per cent. of the patients operated on. Corder, of Kansas City, has collected 232 instances of postoperative thrombosis from the literature, in 213 of which the left saphenous or left femoral vein was involved. He estimates that

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thrombosis occurs in about 2 per cent. of all abdominal operations. The subject has been considered in this country by Vander Veer,[1] Meyer, John G. Clark,[2] and Seibt.[3] The complication has attended operations for a great variety of abdominal conditions, some septic, others free from evidences of infection. It has been noted after perforating gastric and duodenal ulcer by English, and after appendicitis, pelvic inflammatory disease, uterine myomata, and ovarian cysts. In some of the instances occurring after septic conditions, like appendicitis or pelvic inflammatory disease, there is good ground for believing that the operation may have had little to do with the complication, for thrombosis sometimes occurs in these conditions without operation. In the non-septic cases, conditions are different. In these patients, according to Clark, the complication seldom appears until after the eighth day, and usually not until the fifteenth. He believes that the thrombosis in this class of cases is not due to sepsis, but to a propagating thrombus of the deep epigastric veins originally produced by the traumatism resulting from operative manipulations, and especially the use of heavy retractors. The evidence furnished by Clark's study of these cases is quite convincing. The late onset of the attack, the uniform absence of fatality, and the slight general symptoms, all speak against a septic origin in these cases. In the instances following operations for septic conditions, however, the etiology is probably not that of extension from a thrombus in the epigastric veins; at any rate, not in all cases. The onset of the thrombosis in such cases occurs sooner after the operation; there is more fever, more marked constitutional and local symptoms, and secondary embolism may occur. In all postoperative thromboses the possibility that the anæsthetic may act as a predisposing factor must be considered.

Thrombosis in Acute Articular Rheumatism.—Cardiac thrombosis is an almost unheard of complication of acute articular rheumatism, although of course small thrombi in connection with the complicating endocarditis are common enough. Eichorst does not mention a single case of arterial thrombosis complicating this disease in his article on peripheral gangrene as a complication of infectious diseases. Venous thrombosis is also infrequent, and some of the cases reported as such are due to the resulting cardiac lesion rather than to the rheumatism, and should be classed with the thromboses of cardiac orgin. Hess[4] has reported 2 cases of extensive venous thrombosis complicating this disease, 1 of which was fatal. In both instances the thrombi were multiple; in 1 both the upper and lower extremities were involved. There appear to be not more than 25 or 30 authentic cases of rheumatic thrombophlebitis in the literature. In the majority of the patients the veins of the lower extremities were involved and the usual picture of phlegmasia alba dolens was produced. Involvement of the veins of the upper extremities is not, however, exceedingly uncommon, and the axillary, subclavian, jugular, and even the vena cava are at times implicated. The process is probably in most instances due to phlebitis. This was definitely proven by histological examination in one of Hess' cases, and similar ones have been reported by Schmidt and by Combemale and Herin.

[1] *American Medicine*, July, 1901.
[2] *University of Pennsylvania Medical Bulletin*, July, 1902.
[3] *Thrombosen und Embolisen nach Perityphlitis Operationen*, Diss., Leipsic, 1906.
[4] *Deutsch. med. Woch.*, 1902, xxviii, p. 465.

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Thrombosis in Tuberculosis.—The occurrence of cardiac thrombi is not very uncommon in connection with chronic pulmonary tuberculosis with marked circulatory enfeeblement. Ruge and Hierokles reported 4 instances in 1778 patients with tuberculosis. In a few cases of this sort tubercle bacilli have been found in the thrombi. Thrombi in connection with endocarditis complicating tuberculosis also occur, but Forel[1] believes that in many of the cases described in the literature as endocarditis this was not present, and that the real lesion was a thrombosis, the thrombi being accidentally infected with tubercle bacilli. Nevertheless, true endocarditis, usually due to terminal infection with pus cocci, is met with, and occasionally the endocardial vegetations show the histological lesions of tuberculosis.

Arterial thrombosis as a clinical complication of tuberculosis, outside of an occasional thrombus in the branches of the pulmonary artery, seems very unusual. Tubercle nodules are found not uncommonly on the intima of the aorta in cases of miliary tuberculosis. The writer has seen 3 such cases. There is very definite evidence, as shown by Gaylord's case and 1 of the writer's, that these tubercles arise from the infection of small parietal thrombi by the tubercle bacillus.

Venous thrombosis is a fairly common complication of pulmonary tuberculosis, and is probably more frequent than is generally supposed, as one of its most striking characteristics in this disease is its insidious onset. The writer had under observation two years ago a patient with thrombosis of the left femoral vein, during the course of which there was an entire absence of pain, and the complication was discovered during the routine examination. Venous thrombosis occurred 20 times in Dodwell's 1300 patients and 19 times in the 1778 cases analyzed by Ruge and Hierokles.[2] Lubarsch found venous thrombosis 25 times in 180 autopsies on tuberculous subjects. The thrombosis is in most instances a late complication, occurring usually within two or three weeks of death. This is not invariably the case, and the French school especially have described an early venous thrombosis in tuberculosis. Women seem to be more subject to this complication than men. Most of the reports state that the lower extremities are most frequently involved. Ruge and Hierokles' figures show that the left femoral vein is involved most frequently, either alone or with the iliac. The right femoral vein, the right iliac and the saphenous veins are less frequently the seat of the disease. Aldrich's series of cases in which the veins of the upper extremities were involved are quite out of the common. The involvement of the veins of the internal organs, as the renal veins, the veins of the prostatic plexus, and the cerebral sinuses, occasionally occurs in tuberculosis.

The time of onset of thrombosis in tuberculosis might be interpreted to indicate that the complication is due to general cardiac and circulatory debility rather than to the tuberculous infection. These thrombi have been, in fact, generally classed as marantic thrombi. Whilst the circulatory enfeeblement doubtless plays an important part, the possibility of a relation to terminal infections must not be overlooked. Both tubercle bacilli and pus cocci have been isolated from thrombi in this disease, and involvement of the vessel walls has at times been noted. Whether all of these thrombi are of infectious origin is, however, an open question.

[1] *Ergebnisse der Allgemeinen Pathologie*, 1904, vol. ix.
[2] *Berliner klin. Woch.*, 1899, Nr. 4.

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Thrombosis in Gonorrhœa.—The number of reports on cases of gonorrhœa with endocardial complications has increased enormously in the last fifteen years and now reaches into the scores. Aside from the thrombi occurring on the diseased valves in such cases, cardiac thrombi in this disease are rare. Arterial thrombosis is also very uncommon, judging from the literature. Venous thrombosis, while not a common complication, is probably not very uncommon. Heller[1] was able to collect 25 cases from the literature up to 1904, and added 1 of his own. A great majority of the reported instances were observed in France; a few have been noted in Germany, England, Denmark, and Belgium. Saxton Pope has reported a case in this country. The writer recently saw a patient in whom a varicose internal saphenous vein became acutely inflamed and thrombosed during the course of an attack of gonorrhœa. The complication attacked men in 70 per cent. of the reported instances, and practically all of the patients were between twenty and thirty years of age. The thrombosis usually occurs in connection with the first attack and during the subacute stage, on the average about four and one-half weeks after the onset of the disease. Frequently joint complications are also present. The veins of the lower extremity are attacked in the great majority of patients. The veins of the upper extremity are occasionally involved, and there may be thrombosis of the cerebral sinuses of which a case has been reported by Leichtenstern. Gonorrhœal thrombosis differs from the usual form associated with the infectious diseases in that the internal saphenous vein is almost three times as frequently attacked as the femoral vein, and in that the right side is involved as frequently as the left side. Occasionally the thrombosis is bilateral. The local veins of the penis are not so frequently involved as the peripheral vessels. The disease has occasionally been noted to result in secondary pulmonary embolism. The process is probably infectious in nature and due either to the gonococcus or pus cocci, although this has never been definitely proven.

Thrombosis in Syphilis.—Both cardiac and arterial thrombosis is very rare in syphilis. The well-known predilection of the disease for the vascular system frequently leads to arterial lesions, but these take the form of obliterating arteritis rather than thrombus formation. In most of the recorded cases of peripheral gangrene accompanying syphilis—and Eichorst was able to collect but 9 instances in 1901—it is evident that an obliterating endarteritis was the responsible lesion. Even in the patients in whom the onset of the gangrene was very acute, this was the case. It is true that in the final stages of such cases thrombosis often occurs in the diseased vessels, but this is hardly comparable to the thrombosis of other infectious diseases. Venous lesions are much less common than arterial ones in this disease, but when they occur are apt to take the form of a thrombophlebitis. Most of the cases have been reported by French observers. The thesis of Collinot contains records of 25 cases, and according to Dieulafoy[2] some 36 instances had been recorded up to 1906. Syphilitic thrombophlebitis is an early complication of the disease as compared to the arteritis. It appears usually in the secondary period, and may even precede the skin eruptions. It differs from that usually following infections in several respects. The veins of the lower extremities are most commonly involved, but the deep veins, as the femoral,

[1] *Berliner klin. Woch.*, 1904, Nr. 23.
[2] *Clinique médicale de l'Hôtel Dieu de Paris*, 1905–06.

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are only occasionally attacked. The veins of the upper extremities, especially those about the bend of the elbow, are not infrequently implicated. In order of frequency the internal saphenous, external saphenous, basilic, and cephalic veins are attacked. Very often only a segment of the vein becomes thrombosed, and recurrences are common. Multiple involvement is by no means rare, and a series of veins may become involved one after the other, with periods of good health between each attack. Symmetrical involvement is sometimes seen. Apparently the thrombophlebitis of syphilis is never complicated by embolism. The lesion is presumably due to the local action of the *Spirochæte pallida*. The organisms have never been found in a peripheral venous thrombosis, but Benda has described them in arteritis of syphilitic origin, and Nattan-Larrier and Brindeau have observed them in luetic phlebitis of the placental vessels.

Thrombosis in Chlorosis.—Cardiac and arterial thrombosis in chlorosis is very unusual. Leichtenstern's figures[1] give only 1 instance of cardiac thrombosis in 86 patients with thrombosis chlorotica. In the same series there are but 3 instances of arterial thrombosis affecting respectively the pulmonary artery, the axillary artery, and the arteria fossa Sylvii. These are the same cases mentioned by Welch in his article in Allbutt's *System*. Venous thrombosis, on the other hand, is a relatively common complication of the disease. According to Eichorst it occurs in 1.6 per cent. of the patients. Von Noorden's statistics show it in 2 per cent. of the cases, while Leichtenstern observed it only 11 times in 1653 patients with chlorosis, *i. e.*, in 0.66 per cent. of the cases. The latter author agrees that his figures are probably too low, as in many patients the lesion may involve deep veins, such as those of the calf, rendering diagnosis difficult. He estimates that thrombosis occurs in about 1 per cent. of chlorotics. Leichtenstern's figures as to the location of venous thrombi in chlorosis bear out those of Welch. They show the veins of the lower extremities involved in 48 out of 86 instances, the cerebral sinuses in 29 instances, and no other situation represented by more than 1 instance. The remarkably frequent occurrence of sinus thrombosis in the published statistics is undoubtedly liable to give rise to a false impression as to its frequency—a fact which both Welch and Leichtenstern emphasize. The occurrence of large numbers of reports of sinus thrombosis in connection with chlorosis is due to the fact that such cases almost all get into the literature because of their rarity and peculiar interest. The condition is undoubtedly quite unusual, for a clinician with so wide an experience as Bramwell states that he has never seen a case. Still, the figures from the Munich Pathological Institute show that chlorosis is the cause of 13 per cent. of all instances of autochthonous sinus thrombosis, and this disease must therefore be considered as the most prominent cause of spontaneous sinus thrombosis, at any rate in women. In chlorotic thrombosis the large veins of the lower extremities are spared more frequently than in most forms of the disease, and the smaller popliteal and calf veins are frequently involved. Leichtenstern's figures show 26 cases out of 51 with involvement of the femoral vein, and 25 in which the veins of the leg were the seat of the thrombus formation. These figures are, however, probably misleading, as many instances are doubtless overlooked or misinterpreted when the deep veins of the calf are involved. Leichtenstern regards the

[1] *Münch. med. Woch.*, 1899, Nr. 48.

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tendency of chlorotic thrombosis to attack the calf veins and the smaller veins of the leg as an important characteristic of the condition. In some patients the thrombosis, on account of the deep-seated situation, remains entirely latent until the development of a perhaps fatal embolism. In only 1 case of Leichtenstern's 86 was a vein of the upper extremity involved alone, although in 2 others vessels of the upper as well as of the lower extremities were thrombosed, 1 of these patients having also a thrombosis of a cerebral sinus. The usual preference for the left leg is shown by Welch's figures, which indicate that the process is bilateral in 46 per cent. of the cases and unilateral in 54 per cent.; 34 per cent. of the total number of instances occur on the left side The marked tendency to bilateral involvement which these figures show is regarded by Welch as an important characteristic of thrombosis chlorotica.

The prognosis of chlorotic thrombosis so far as recovery of the patient is concerned is, as a rule, fairly good, if we except those cases in which the thrombosis involves the cerebral sinuses. Even these cases, however, are not universally fatal, and since the cases of Bristowe and Buzzard were reported 2 others have been recorded by English observers in which undoubted signs of sinus thrombosis were followed by recovery. In the occasionally severe cases involving the vena cava recovery may also occur, as an instance reported by Weinberger shows. The thrombi occurring in the extremities give rise to emboli in 20 per cent. of the patients according to Leichtenstern, a very high percentage compared with most other forms of thrombosis. Welch found evidence of secondary embolism in 25 per cent. of his series. The emboli practically always lodge in the branches of the pulmonary artery, and in a large percentage of the patients a fatal result ensues. Leichtenstern believes that thrombi in chlorosis are broken up with unusual ease, his explanation being that they are largely composed of blood platelets which are known to be increased in this disease. Doubtless, too, the fact that many of the patients are not bedridden and that the thrombosis is often latent increases the chances of embolism. In the bedridden patients with femoral thrombosis the embolism has usually followed some muscular effort, and it would seem from this that, although exercise plays a part, the main element of danger lies in some peculiarity in the thrombus itself. It is clear that thrombosis chlorotica is of much graver import than most forms of thrombosis, the puerperal form excepted.

The nature of chlorotic thrombosis is still obscure. Numerous theories have been evolved to explain it, some incriminating the feeble circulation; others supposing some degenerative or inflammatory vascular lesion; still others assuming chemical or morphological changes in the blood itself. Welch believes that there are good reasons for considering the increase in blood platelets of importance in thrombosis chlorotica, and Leichtenstern also lays a good deal of stress on this factor. Possibly the intimal changes in the vessels long ago described by Virchow may also play a part. Welch suggests that the peculiarities in the circulation which give rise to the venous hums so common in this condition may also lead to the production of whirls and eddies which favor thrombosis. The infectious theory of thrombosis has been advanced by some to explain thrombosis chlorotica, but there is no weighty direct evidence in its favor.

Thrombosis in Other Infectious and Cachectic Conditions.—Thrombosis has been occasionally described in a variety of infectious and cachectic

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conditions other than those specifically considered, but not often enough to warrant special consideration. In dysentery, for example, both arterial and venous thrombosis is occasionally met with, and has been described by Laveran, and more recently by Haasler.[1] Eichorst only records 1 very old observation of gangrene in dysentery, but Haasler notes 2 cases occurring in his own series, 1 following thrombosis of the femoral artery, and the other thrombosis of both arteries of the arm. In chronic diarrhœa also, especially in feeble infants and old people, thrombosis is occasionally noted. In cholera Asiatica, diphtheria, erysipelas, chronic suppuration, plague, measles, peritonitis, dental caries, Bright's disease, anæmia, and scarlet fever occasional instances of thrombosis are reported. In Bright's disease thrombosis is most apt to occur in chronic nephritis with arteriosclerosis and cardiac failure, and in the amyloid kidney. Typhus fever is the infectious disease most commonly associated with arterial thrombosis, but is so rarely seen in this country that extended notice seems unnecessary. A collection of the reported instances may be found in Eichorst's article. Thrombosis after malaria, both venous and arterial, has been reported, but there is doubt in a good many instances whether the diagnosis of malaria was correct. Laveran has described 1 instance of gangrene of both legs in this disease, possibly due to arterial thrombosis. Futcher[2] reports the only instance of thrombosis in malaria seen in over 2000 cases of the disease observed in Osler's clinic. In this case, even, it was doubtful whether the malaria really caused the thrombosis, as the patient was anæmic and also suffering from nephritis. The multiple thrombi which occasionally occur in gastric cancer and to which the French school attach some diagnostic significance are so unusual that they need merely be mentioned. In all forms of malignant new-growth, however, thrombosis is not unusual, as shown by the statistics of Mannaberg and Haward. Mannaberg's figures show that about 20 per cent. of all thromboses are associated with neoplasms. Haward's table places the figures at 13 per cent.

The cause of these cachectic thromboses is probably not always the same and depends to some extent on the character of the primary disease. Many of these thrombi, especially those occurring in connection with neoplasms, asthma, and chronic nephritis, occur in old people in whom disease of the blood vessels is often already present. Other instances occur under conditions associated with great enfeeblement of the circulation, and, in still others, changes in the blood itself, such as lysis of red blood corpuscles or increase in the blood platelets may predispose to thrombosis; finally, terminal infection doubtless plays a part in some instances.

Thrombosis in Cardiac Disease.—The thrombi which occur in the heart itself during the course of cardiac disease are of anatomical rather than clinical interest, and are best considered under the pathology of thrombosis. Arterial thrombosis may occur during the acute stages of endocarditis, although embolism is much more common. The writer has found no record of arterial thrombosis in chronic heart disease with failure of compensation. Thrombosis of the pulmonary vessels is relatively common in uncompensated valvular lesions, but is often of no clinical significance, as the vessels involved are usually small ones. Peripheral venous thrombosis is not very frequent

[1] *Deutsch. med. Woch.*, 1902, Nr. 3.
[2] *Johns Hopkins Hospital Bulletin*, 1900, vol. xix, p. 49.

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if we judge from the literature, but is perhaps, as Welch[1] suggests, not infrequently overlooked. It differs in some respects from the type of venous thrombosis which is associated with the common infectious diseases. Welch collected, up to 1900, 28 instances of peripheral venous thrombosis in uncompensated heart disease, but the condition is certainly more common than these figures would indicate, as no less than 6 other cases were mentioned in the discussion of Welch's paper. His analysis shows that this complication attacks females more often than males, occurs most frequently between the ages of fifteen and thirty, and is almost always associated with lesions of the mitral valve. The thrombi are formed, as a rule, only in the advanced stages of cardiac insufficiency, the frequent concurrence of pulmonary infarcts being collateral evidence of this. The most remarkable peculiarity of the peripheral thrombi in cardiac disease is their location, which differs from all other forms in the great preponderance of the involvement of the vessels of the upper extremities. In 16 out of Welch's 28 cases the thrombosis involved the veins of the neck and arms; in 7 it was limited to the arm veins, and in 1 to the veins of the neck. In a great majority of instances more than one vein was involved, the commonest combination being a continuous thrombosis of the innominate vein, the internal and external jugular veins, and the subclavian and axillary veins. The left side was attacked in 22 out of the 24 patients, and there were 7 instances of bilateral involvement. Clinically the patients with thrombosis presented the usual signs and symptoms except that in a certain number the thrombosis was latent, being masked by the symptoms of failing compensation, and especially by the extensive œdema. Most of the patients succumbed, as would be expected, inasmuch as the thrombosis in these cases is usually evidence of marked failure of compensation.

The cause of thrombosis in cardiac disease is still a subject of discussion. The peculiarity in localization suggests a local etiological factor; possibly there is a developmental error in connection with the valves near the junction of the internal jugular and subclavian veins on the left side. Hirschlaff claims that this is the case, and McMurrich has recently shown that a similar condition exists on the left side in connection with the iliac vein. The pressure of the dilated left auricle as an important factor in causing the peculiar localization of the thrombosis must certainly be taken into consideration, as it may be sufficient to cause a diminution in the left radial pulse and has in some instances even caused a paralysis of the left recurrent laryngeal nerve. The unusual opportunity for the formation of eddies on account of the structural peculiarities of the bulb and valves of the internal jugulars is also doubtless a strong predisposing factor—an opinion which Welch emphasizes. Welch seems to think that the most probable exciting factor in this class of cases is the terminal infection which is so common in chronic heart disease.

Thrombosis in Gout.—It seems certain that two types of thrombophlebitis occur in connection with gout. In one, typical examples of which have been described by Garrod and others, the complication occurs during the gouty attack, is probably the result of local overuse, and accompanies gout in the feet, affecting the veins of the lower limbs on the side involved by the gouty attack. The thrombophlebitis in these patients seems to be due to a direct

[1] Jacobi's *Festschrift*, 1900.

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extension of the gouty inflammation to the veins, and such cases are properly classed as gouty thrombosis.

The second type of cases occurs, according to Paget, "with little or no provocation, in persons of marked gouty constitution or with gouty inheritance." When we consider the liberal interpretation of the term gout as used by English writers and remember that cases are reported presenting symptoms exactly similar to those Paget describes, but in patients who give no evidence of gout or gouty inheritance we are justified in assuming that the term "gouty phlebitis" has been used too indiscriminately. This second type would better be described, as Briggs[1] suggests, as *idiopathic recurrent thrombophlebitis*. The tendency to this form of thrombosis is apparently in some cases hereditary, as in 1 of Paget's patients, and in Tileston's case, or, as in 1 of Briggs' patients, there may be a family tendency to arterial disease. The condition manifests several peculiarities which distinguish it from most types of thrombophlebitis, although it resembles in a good many ways the form occurring in secondary syphilis. It attacks almost always the superficial veins of the lower limbs, involving short segments of vessels rather than entire trunks, tends to recur and involve new segments of the vessel originally attacked, occurs without definite cause, and gives rise to comparatively little local or general reaction. The left side appears to be more often involved than the right, although the cases on record are too few to judge of this with certainty. The veins of the upper limbs are occasionally implicated. The danger from secondary embolism in this form of thrombosis does not seem to be great, judging from Briggs' experience, but Daguillon states that the prognosis is grave owing to the facility with which embolism occurs. As the name implies, the etiology of this form of thrombosis is obscure, but in view of T.C. Janeway's findings in Schwyzer's patient, chronic fluorine poisoning must be eliminated before a diagnosis of idiopathic thrombophlebitis is made.

Primary Infective Thrombosis.—There are a few records in the literature of patients in whom the clinical picture of general sepsis was accompanied by widespread thrombus formation, both in the veins and arteries, but usually with either venous or arterial thrombosis predominating. That such cases are not of more frequent occurrence is remarkable when we consider the frequency of endocarditis, to which they are comparable, and the close analogy between the endocardium and the intima of the bloodvessels. There is evidence, however, that, in some instances at any rate, the primary lesion is not in the intima, but that the infection is carried by the vasa vasorum. Clinically the most striking feature in some of these patients is the absence of symptoms and physical signs at all comparable in severity to the vascular lesions. In the patients of Dowse and Osler, abstracts of whose histories may be found in Welch's article, this latency of symptoms was not very marked, as the peripheral vessels were the ones mainly involved. In the very remarkable cases of Eichorst[2] the lack of marked symptoms on the part of the internal organs was a striking feature. In 1 of his patients, a woman of forty-one, mitral endocarditis of the verrucose type was found grafted on an old endocardial lesion, but this was entirely incapable of accounting for the multiple thrombi and emboli. Thrombi were found in

[1] *Johns Hopkins Hospital Bulletin*, 1905, vol. xvi.
[2] *Deutsch. Arch. f. klin. Med.*, 1904, vol. lxxx.

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this instance in the splenic, left renal, superior mesenteric, both common iliac, both femoral, the left common carotid, and the left superior thyroid arteries and the abdominal aorta. There were also thrombi in the right pulmonary artery and the inferior vena cava, and numerous infarcts in the lungs, spleen, and kidneys. In this patient, as will be noted, the arteries were mainly involved. In the second patient, a girl of fifteen, the veins were mainly attacked. There was thrombosis of the right external jugular vein, the right innominate vein, the superior vena cava, the left internal jugular vein, the left axillary vein, the branches of the right pulmonary artery, the splenic vein, both renal arteries and renal veins, the mesenteric veins, the portal vein, the inferior vena cava, and both iliac veins. Eichorst's examination of the vessels in the first case led him to believe that the process was a sepsis in which, as the result of bacterial infection through the vasa vasorum, localized areas of arteritis with thrombus formation were produced. Whether this is always the pathway of infection in this form of thrombosis is not clear. It is possible that in some instances the infection may occur through the intima by means of the blood circulating in the interior of the vessels.

Special Pathology.—Structure of Thrombi.—The differences in appearance which characterize the several varieties of thrombi depend upon the relative proportions of the various elements entering into their constitution. In the common varieties of thrombi the plug is constituted of the formed elements of the blood, the red and white corpuscles, and the platelets, plus fibrin. The main factor which decides the appearance and structure of such thrombi is the physical condition of the blood stream at the time the thrombosis occurs. If the process involves stagnating blood, a red or cruor thrombus occurs. If the blood is still circulating, a white thrombus results. Mixed thrombi occur when, during the formation of a white thrombus, the circulation is markedly impeded or stopped, so that portions of the plug are composed of stagnating or almost stagnating blood, or they may occur from fissuring of a white thrombus with a formation of red thrombi in the fissures.

Thrombi are apt to be confounded with postmortem clots, the distinction between the two being, however, usually not very difficult. The postmortem clot is common in the cavities of the right side of the heart, in the cerebral sinuses, and in the veins. It may be entirely red, or, what is common in the heart especially, mixed red and yellow, the yellow portion often having a striking resemblance to chicken fat. In the heart such clots often penetrate between the columnæ carneæ, giving a false impression of being adherent, but are easily detached and with very little experience can be distinguished from true mixed or white thrombi which are usually so firmly adherent that they cannot be removed without tearing. In the vessels also, postmortem clots which are partly yellow and partly red may be formed and may be taken for mixed thrombi. In this instance the red portion of the clot is the dependent portion, and here again the clot, as distinguished from the true thrombus is easily detached from the vessel wall. The grayish color and opaque appearance of the white thrombus is usually quite different from the yellowish color and semi-transparent appearance of the postmortem clot. The consistency of the two is different, the postmortem clot being elastic and homogeneous, the thrombus granular and rather friable. The peculiar ridging of the surface of certain thrombi is never seen in post-

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mortem clots. These remarks refer particularly to the white or mixed thrombi. Red thrombi when recently formed may be much more difficult to distinguish from postmortem clots. Usually in red thrombi the deposition somewhere on the surface of a white film composed of leukocytes, platelets, and fibrin serves as a point of differentiation. In older red thrombi the marked adherence to the heart or vessel wall and the granular consistency render differentiation easy.

Microscopically red and white thrombi differ considerably in structure. Red thrombi are composed of the formed elements of the blood, in approximately their normal proportions, traversed by fine strands of fibrin. White thrombi are made up of a framework of granular material composed of fused blood platelets, in the meshes of which are red and white corpuscles and fibrin in proportions which vary according to the rapidity of the blood stream at the point of thrombus formation. Leukocytes are usually present in good numbers, especially along the edges of the platelet network, and fibrin threads occur mainly among the leukocytes. Red corpuscles are not numerous if the circulation was rapid when the thrombus formed, but may be present in large numbers if the circulation was feeble. It is on the surface of white or mixed thrombi that the transverse ridges, described especially by Zahn, may be seen. They run at right angles to the long axis of the vessel, lie roughly parallel to one another, and may be united by fine oblique striations. The appearance is due to a physical action of the circulating blood upon the viscous surface of the thrombus similar to that produced on the sand of river banks or the seashore by the lapping of the waves.

Method of Formation of Thrombi.[1]—Different ideas have been held at various times as to the nature of thrombus formation. Briefly stated, the two main views have been:

(1) That it is merely a process of coagulation. (2) That the essential process is an agglutination of the blood platelets with which coagulation is associated as a secondary process. The idea that thrombosis is coagulation pure and simple has now been abandoned by most pathologists; at any rate, so far as the formation of the more common white or mixed thrombi is concerned. The generally accepted view as to the formation of such thrombi based upon experimental work and the study of human lesions, indicates that the first step in the thrombus formation is the accumulation of blood platelets at the point where the lesion occurs. This is followed by the transformation of the platelets into a sticky mass (viscous metamorphosis) which causes them to adhere to one another and to the vessel wall. Later polynuclear leukocytes accumulate in the interstices of the mass, and fibrin appears. Red corpuscles are present in numbers varying inversely to the rapidity of the blood current at the site of thrombus formation. The latter part of the process is believed to involve the ordinary changes which accompany coagulation. There has been some opposition to this view of thrombosis in recent years, Gutschy having claimed that the first step was the deposition of a very fine fibrin film at the site of thrombus formation. His views have not been confirmed by most observers, and the very interesting comparative studies of L. Loeb, showing that the process of agglutination is a widespread one among all the forms of life, much more so than coagula-

[1] L. Loeb, *Virchow's Archiv*, 1906, vol. clxxxv.

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tion, strongly favor the view that the accumulation of the platelets is the primary process.

The manner of formation of the agglutination thrombi composed of red blood corpuscles which occur, as previously mentioned, in connection with certain infections and intoxications, has been described by Flexner. The red corpuscles fuse as a result of the action of the poison into a dark, soft, conglutinated clot, the fluid portions of the blood being laked in appearance. Sections of experimental clots produced by the intravenous injection of ether, show agglutination of some of the red blood corpuscles, others appearing as shadows. Fibrin is not present in these experimental clots. In man such agglutination thrombi are made up of conglutinated masses of red cells with a few leukocytes, usually along the walls of the vessels, and but little fibrin. There seems now no doubt that in the later stages of such thrombi, transformation of the fused mass occurs, and the appearance is then that of the so-called hyaline thrombi. The view of Klebs that a certain type of hyaline thrombi are derived from fused red blood corpuscles seems fully substantiated.

Accepting Welch's definition of a thrombus as a plug formed during life from constituents of the blood, we must recognize two other varieties of thrombi which occur occasionally, viz., leukocyte thrombi and fibrin thrombi. Welch expresses the opinion that the formation of ordinary white thrombi from leukocytes, if it occurs, must be a rare event. In connection with local inflammatory lesions, however, a plugging of the regional vessels with leukocytes is not uncommon. Thrombi composed of fibrin from the beginning, as distinguished from old thrombi which have undergone fibrinous transformation, occur merely in small vessels and are devoid of clinical interest. They have been described in the smaller vessels of the lung in connection with pneumonic processes, and Herzog[1] has described them in the glomerular vessels of the kidney in bubonic plague. Fibrin thrombi at times undergo transformation into hyaline material constituting one variety of hyaline thrombi.

Growth of Thrombi.—Most vascular thrombi when they originate do not completely fill the vessel, but lie along one side of the tube constituting mural or parietal thrombi. In the cavities of the heart parietal thrombi are the rule, and are usually in the form of rounded or flattened masses projecting into one of the heart cavities. The auricular appendage may be completely filled with a thrombus mass, and a polypoid continuation into the auricular cavity is not uncommon. When, as occasionally happens, a thrombus becomes free in the auricle it may assume a globular form, and then constitutes a so-called ball thrombus. The vascular thrombus does not as a rule remain parietal, but ultimately fills the vessel, occluding the lumen (occluding or obstructing thrombus). It then usually extends, commonly in the direction of the blood stream, occasionally in an opposite direction. As a rule the extension ceases when the first branch of the vessel capable of re-establishing the circulation is encountered; but this is by no means always the case, and thrombi may extend into the branches or may be continued on one wall of the vessel beyond the branch as parietal thrombi. When prolongation of the thrombus occurs, the extended portion is often much less adherent to the vessel wall than the original thrombus, and the terminal end

[1] *Bulletin No. 23, Bureau of Government Laboratories*, Manila, 1904.

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of the growing thrombus is usually cone-shaped and entirely free in the blood stream. A marked extension of the thrombus seems more apt to occur in veins without valves, although this is not invariably the case. There is some reason to believe, too, that infective thrombi are more liable to extend widely than aseptic ones.

Secondary Changes in Thrombi.—The most important of the secondary changes which occur in thrombi is the process of organization, during the course of which the thrombus is replaced by newly formed connective tissue. The process is essentially the same, whether the thrombus is a red or a white one, and whether it occurs in the heart or the vessels. Certain minor differences of no vital importance have been described between organization in red and in white thrombi, especially by the French school. In organization the active participants are the endothelial cells lining the vessel or heart, the connective-tissue cells of the cardiac or vascular wall, and the vasa vasorum. The process is often preceded and usually accompanied by degenerative changes in the thrombus, transformation of the platelet masses into a granular material, degeneration of the leukocytes, decolorization and disintegration of the red corpuscles with hæmatoidin formation, increase in and coarsening of the fibrin strands, and more or less retraction and fissuring of the thrombus mass. In the actual process of organization the thrombus plays a passive part, acting for the time as a temporary scaffolding for the advancing vessels and connective-tissue cells, ultimately being removed, mainly by phagocytosis. The process consists in the vascularization of the clot by newly formed vessels which are pushed in as sprouting processes from the preëxisting vasa vasorum, and which are accompanied by newly formed connective-tissue cells originating either from those preëxisting in the vessel wall or from the actively dividing endothelial cells of the intima. These proliferated intimal cells coat over the surface of the thrombus which is exposed to the blood stream, penetrating into the crevices and crannies formed by the retraction or fissuring of the clot. According to some observers newly formed vessels may also originate from the endothelial cells. The process results in replacing the thrombus by connective tissue, at first vascular and made up of an embryonic type of cell, later becoming fibrous and poor in vessels like cicatricial tissue. The ultimate result so far as the vessel is concerned may be a completed plugging with transformation of the thrombosed area into a fibrous cord, or more commonly a partial or even complete restoration of the circulation, either as a result of retraction of the organized thrombus or the formation through it of a series of blood channels uniting the circulation on either side. Occasionally a complete disappearance of the organized thrombus occurs, or it is represented by a few fine, thread-like adhesions which in no way interfere with the circulation.

The rapidity with which organization of the thrombus takes place is a matter of considerable practical importance, as the danger from secondary embolism gradually decreases as organization progresses. Just as in the process of wound healing, so in organization, there are great individual differences in the capability of repair. In favorable cases organization may be well under way, according to Welch, within a week. There are, however, certain factors which may delay organization, and the most important of these are infection, infected thrombi organizing much less rapidly than aseptic ones, and disease of the heart or vessel wall. The importance of the latter factor can be realized when it is remembered that the process

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of organization proceeds from the tissues of the cardiac or vascular parietes. Under certain circumstances salts of lime are deposited in thrombi, more especially in venous thrombi. Rarely the calcified thrombus in its original form is transformed into a stony cylinder; more commonly calcified thrombi are in the form of spherical calcific nodules with smooth surfaces lying in the vein or artery almost free from attachment, and constituting phleboliths or arterioliths. The vein-stones are much the more common, look like small seed pearls, and are most often met with in varicose veins, in the veins of the spleen, and in the smaller pelvic veins, especially those about the base of the bladder.

Secondary degenerative changes in thrombi in the form of liquefaction or softening are of great practical importance on account of the increased danger from secondary embolism which is associated with them. In most works on pathology two forms of softening are recognized, the bland and the infective, the latter form being again subdivided into purulent and putrid softening. This subdivision is based on the assumption that certain of the softened thrombi, *i. e.*, those classed as bland, are bacteriologically sterile, while the others are infected. The work of Harris and Longcope in Welch's laboratory and Widal's researches on puerperal thrombosis have shown that bacteria are present in quite a large percentage of apparently bland thrombi, and this is often true even when no softening is present. Whether the softening of bland thrombi is due to infection is still an open question. The French school strongly favor the supposition that the softening is due to bacterial action. From a clinical standpoint there is no question that emboli originating from softened thrombi do not all give rise to similar results, those from bland emboli causing a temporary febrile reaction and being comparatively harmless, whilst those from septic thrombi cause serious metastatic inflammations. It is possible that the bland softening is the result of an attenuated form of infection, although the fact that the escape of softened material into the circulation causes febrile reaction is not necessarily evidence that infection is present. It is known that thrombi contain constituents originating from the blood itself which are capable of producing fever when introduced into the circulation. Of the definitely infective thrombi, the putrid differ from the purulent in that they are due to bacteria of putrefaction as distinguished from the ordinary pathogenic cocci.

Puriform softening is most common in cardiac thrombi, but may result in those occurring in peripheral vessels. In the so-called bland softening the liquefied material has to the naked eye the appearance of more or less blood-stained pus. The microscope shows that the puriform material is made up of the debris of the constituent elements of the clot, granular and fatty particles, blood pigment, crystals of fatty acid, and more or less degenerated red and white blood corpuscles. In the infective thrombi the softened area has the appearance of true pus and contains under the microscope numbers of polynuclear leukocytes and bacteria. In putrid softening the thrombus is of a greenish or brownish color, and the liquefied area has an offensive odor similar to that encountered elsewhere in association with gangrenous processes.

Localization of Thrombi.—*Cardiac Thrombi.*—Two types of cardiac thrombi are to be observed, the mycotic thrombi, usually of small size, associated with endocarditis, and the larger thrombus masses found in the cavities of the heart in connection with conditions of an infectious or cachectic

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nature or associated with enfeeblement of the circulation. The mycotic thrombi being directly due to endocarditis, usually occur on the valves, but are occasionally mural. The second type of thrombi, which occur especially in chronic heart disease with failure of compensation and dilatation of the cavities of the heart, are met with in those situations where the circulation is slowest and where the physical conditions favor the formation of eddies. Such conditions are found especially in the auricular appendages and in the apices of the ventricles between the columnæ carneæ. The peculiar cardiac thrombi known as ball thrombi, almost invariably occurring in the left auricle in association with mitral stenosis, are due to the detachment of portions of mural thrombi which become molded to a spherical shape through accretion and constant rotation in the auricular cavity. They are of pathological rather than clinical significance, and a full discussion of their pathogenesis may be found in Welch's article in Allbutt's *System*. The same remark applies to the curious pedunculated cardiac polyps occasionally described in the literature which usually spring from the septum of the left auricle. Some of these are undoubtedly true organized thrombi; others are probably the result of intramural hemorrhage or are varicosities of the veins of the septum.

Arterial thrombi, which are most commonly associated either with chronic arterial disease or acute arteritis of an infectious nature, may occasionally accompany debilitating diseases or may be due to the direct effects of trauma. They occur most frequently in the arteries of the extremities, more particularly those of the legs, and involve the two sides of the body with almost equal frequency. The visceral arteries, especially those of the lungs, brain, heart, and intestines, are not infrequently involved, and sometimes main trunks like the aorta become thrombosed.

Venous thrombosis is by far the most frequent variety, as the mechanical and chemical conditions favoring thrombus formation are most frequently met with in the venous circulation. These conditions have been summarized by Welch as "the slower mean speed of the blood in veins than in arteries; the low blood pressure; the flow from smaller into larger channels; the absence of pulsation; the presence of valves; fixation of the venous wall in certain situations to fasciæ and bone; the existence in some places of wide sinuses and ampullar dilatations; the agency of certain subsidiary forces, such as muscular contractions and movements of the limbs, in assisting the flow in the veins; the composition of venous blood, particularly the rich content of CO_2, and perhaps the functions of the capillaries and small veins in the production and absorption of lymph."

Venous thrombi are found with the greatest frequency in the veins of the lower extremities, both superficial and deep, and the small pelvic veins, and in the cerebral sinuses. Thrombi in the veins of the arms are met with, as has already been stated, especially in chronic non-compensated heart disease, and thrombi in the pulmonary veins are occasionally described. The venæ cavæ are, as a rule, only involved secondarily by the propagation of thrombi into them from their branches. A striking peculiarity of venous thrombosis is the marked tendency, both in the upper and lower extremities, to the involvement of the veins of the left side. This peculiarity is probably not due to a single cause, but to a variety of factors. The causes generally adduced in connection with the lower extremity have been the greater length and obliquity of the left common iliac vein, its situation beneath the right

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common iliac artery, and the exposure of the vein on this side to pressure from the distended rectum or sigmoid flexure. The recent researches of McMurrich[1] indicate that there is another important factor hitherto overlooked. This observer found in 10 out of 31 cadavers a localized adherence of the anterior and posterior walls of the common iliac vein just below its termination in the inferior vena cava. In 9 of the 10 cases in which this anomaly was found it occurred on the left side. McMurrich thinks it due to a developmental error. In like manner Hanot and Parmentier ascribe the frequency of left-sided thrombosis in the veins of the upper extremities to an interference with the return flow of blood resulting from the greater length and obliquity of the left innominate vein. In the upper extremity Hirschlaff has described developmental errors in connection with the valves near the junction of the internal jugular and subclavian veins analogous to those described by McMurrich in connection with the iliac veins, and, like them, much more frequent on the left side. *Capillary thrombosis* is of pathological significance only, and practically never occurs except in direct association with local inflammatory conditions, under which circumstances the capillaries involved in the process usually become plugged.

Local Effects of Thrombosis.—The local effects of thrombosis depend mainly upon the degree in which the circulation is obstructed by the thrombus. In cardiac thrombosis and in thrombosis occurring in saccular aneurisms there is usually no marked disturbance of the circulation, and there may be little or none from parietal thrombi in vessels, provided the vessel is a large one and the thrombus small. In the great majority of arterial and venous thrombi there is serious interference with the circulation, and the result depends mainly upon two factors: the rapidity with which the vessel is closed, and the number of collaterals entering the area whose nutrition is cut off. In the case of peripheral vessels the rapidity of closure is the more important factor, as the vessels are usually well supplied with collaterals and there is free anastomosis. In the case of internal organs the character of the circulation is more important, for some organs have a terminal circulation in the anatomical sense and in others the amount of anastomosis is so slight that there is practically no chance for the formation of a collateral circulation. The gradual obliteration of an artery or vein by thrombosis is usually devoid of any result save the gradual development of a collateral circulation, although in some instances complete plugging of an artery, even though gradual, may result in effects similar to those produced by a sudden stoppage of the circulation. The changes occurring from sudden stoppage of arterial blood supply from thrombosis are the same as those produced by embolism, and are so much more frequently the result of the latter complication that they are best considered under that head. Where obliteration of a vein of any size occurs suddenly, the most striking change is a venous or passive congestion followed by the escape of the blood serum into the tissues or the cavities of the body. There are records of rare instances in which thrombosis of the large venous trunks, such as the femoral or axillary, has been followed by gangrene. Förster[2] has reported several such cases. Most of the patients in whom gangrene has occurred have been the subjects of uncompensated cardiac disease with extreme feebleness of the circulation. Gangrene probably occurs under these conditions because the feeble heart

[1] *British Medical Journal*, December 15, 1906.
[2] *Wien. klin. Woch.*, 1904, Nr. 44.

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is unable to force the blood through the collaterals, and this may be rendered still more difficult by the presence of œdema. In some patients with gangrene following venous thrombosis there is evidence that complicating arteriosclerosis probably played a part. In patients with thrombophlebitis there occur, besides the purely mechanical effects of stoppage of the circulation, the local evidences of inflammation with the usual clinical picture. In some instances, where the infection is intense, actual abscess formation about the thrombosed vein results. This is rather unusual in connection with the peripheral vessels, but is common enough in some situations, as, for example, in the branches of the portal vein.

Symptoms.—The symptoms produced by the formation of a thrombus will depend to some extent on the same factors which influence the effects of the process on the tissues, viz., the rapidity with which the circulation is cut off and the extent of the collateral circulation in the affected tissue. Certain local peculiarities in the vascularization of organs and in the sensitiveness of their cells to interference with their blood supply are also factors in causing variation in the symptoms. There is a certain percentage of thrombi in the peripheral vessels associated with gradual occlusion of the lumen which produce no symptoms whatever, and thrombi in the vessels of the internal organs are frequently latent or give rise to no clinical signs which permit of a diagnosis.

Von Schrötter divides the symptoms of thrombosis into those which are directly due to the formation of the thrombus and those which result from its effect upon the blood supply. Of the former group pain is the most prominent, of the latter œdema or fluid in the cavities of the body. General symptoms, such as febrile reaction and quickened pulse, are also common. The pain may accompany either bland or septic thrombi, and is probably due to the action on the nerves of the affected vessels of pressure, or, in infective cases, of irritating toxins. The cause of the œdema has been and is still the subject of much discussion. It is certain that it is not always of the same nature, being sometimes due to venous stasis and sometimes of an inflammatory nature. The most prominent factors in the production of the œdema from stasis are, according to Welch, the increased intravenous and intracapillary pressure, increased permeability of the capillary walls, diminished absorption of lymph, arterial dilatation, and sometimes an hydræmic condition of the blood. The symptoms of thrombosis vary so much according to the situation of the thrombus that it is necessary to consider the more prominent forms in detail.

Peripheral Venous Thrombosis.—Peripheral venous thrombosis is the most common variety, and as the femoral vein is the most frequent site of the process, thrombosis of this vessel will be described. In a typical case both general and local symptoms are present.

The general symptoms often precede the local ones, and the onset of the attack is at times a definite rigor. More commonly there are chilly sensations followed by fever and perhaps sweating, and an increase in the rapidity of the heart's action. The fever in patients with bland thrombi is not usually high, 101° to 102° F., in an average case; in infective thrombosis it may be much higher, 104° or 105° F. Sweating is a rather common accompaniment of the fever, but is not always present. Examination of the blood at the onset of the thrombosis will often show a pure leukocytosis, although in diseases like typhoid fever, where a leukopenia is the rule, the rise in the

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number of leukocytes may be slight or lacking. The rapid heart action may precede the fever by several days, and at all times the pulse rate is apt to be disproportionately rapid. The appearance of a step-like rise in the pulse rate (kletter-pulse) as a premonitory sign of thrombosis may occur in connection with peripheral thrombi, and is known to the Germans as Mahler's sign. Occasionally these general symptoms precede the local symptoms by several days, but as a rule local signs appear coincident with or shortly after the constitutional disturbance, and quite commonly the local symptoms are the first to attract attention.

The most prominent local symptom at the onset of thrombosis is *pain*. In femoral thrombosis this often appears first in the calf, although it may be present from the beginning at the site of thrombus formation. The pain is often intermittent at first, but gradually becomes a constant feature. It may not be very severe, but may be intense, and is described sometimes as burning or boring, sometimes as cramp-like. At first localized, it usually becomes more general as the disease progresses. Frequently the patient complains of a feeling of tension and weight in the limb. The pain is associated with tenderness of the affected member, most marked along the course of the thrombosed vessel, which can often be rolled under the fingers as a firm, sensitive cord. In spare individuals with thrombosis of superficial veins the course of the vessel may be traceable as a dull, red line on the overlying skin, usually rather wider than the diameter of the vein. Disturbances of sensation are uncommon in venous thrombosis, aside from feelings of numbness and formication. In some patients, however, there may be intense neuralgic pains, especially in the domain of the sciatic nerve, as described by Vaquez and Quénu, and these are apparently due in some instances to a definite neuritis. Disturbance of motion is usually present, probably due more to the natural tendency of the patient to immobilize the limb on account of pain than to true paralysis. The older writers on the subject, Graves especially, speak as though true paralysis was almost constantly present, but modern observation does not favor this view.

Œdema is the second prominent local symptom. Like the pain, it may appear first in the region of the calf and gradually extend upward, but in patients in whom infective thrombosis is present and in whom inflammatory œdema predominates, it may begin about the site of thrombosis and extend toward the periphery. The degree of œdema varies considerably; it may be very slight, but in well-marked femoral thrombosis is generally a prominent feature. Its character varies to some extent with the type of thrombosis; in patients with marantic thrombosis or with mild thrombophlebitis the affected limb is usually pale, with a glossy skin, and cooler than its fellow. Occasionally there is marked cyanosis, and frequently the superficial veins are dilated. In the severer infective types of thrombophlebitis the skin may be reddened, and the surface temperature of the affected limb may be considerably higher than that of the unaffected one. The œdema does not usually pit like the œdema of heart and kidney disease, but is firm and elastic.

In atypical cases there may be considerable variation from the above picture. The affection may be entirely latent. Almost any of the symptoms and signs may be absent. The constitutional symptoms, especially in old, feeble individuals with cachexia, may be entirely lacking. The pain may be absent, or may be so slight that it is entirely disregarded or attributed

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to some other cause. The œdema may be so slight that it is overlooked. It is usually in thrombosis of the deeper and smaller veins, such as those of the calf, that the entirely latent forms occur. Thrombosis of larger veins may be disregarded by the patient, but will usually be discovered by a careful observer. The signs may be masked, as in cardiac disease, by changes like œdema due to the original malady. On the other hand, the general symptoms, especially in the primary infective thromboses, may be intense and partake of the character of a violent sepsis.

The *course* of peripheral venous thrombosis varies considerably with the nature of the exciting cause and of the disease which preceded this complication. In cases associated with severe sepsis or with the terminal stages of debilitating diseases, death often takes place before a chance for retrograde changes is offered. In the ordinary thrombosis accompanying infectious diseases, in which recovery follows, the acute symptoms usually begin to subside by the end of the first week, the pain and tenderness become less severe after four or five days, the œdema becomes less marked, and the fever and constitutional symptoms abate. Where the local infection is severe the subsidence of active symptoms is often much slower. The lasting effects upon the limb will be considered under complications. The thromboses of the upper extremities are often less severe and recover more quickly than those of the lower extremities.

The *diagnosis* of peripheral venous thrombosis is, in characteristic cases, a simple matter. The sudden onset with localized pain, the palpable tender vessel, the evidence of disturbance in the venous circulation, and the œdema make recognition easy. In patients with thrombosis of small, deep-seated veins, where the vessel is not palpable and there is no marked œdema, the diagnosis may be more difficult. The differentiation from embolism will be discussed under that head; it is only necessary to say here that in thrombosis the arterial pulsations can still be felt, and that gangrene, so common in embolism, is very rare in thrombosis. Bennett[1] has described a type of disease which appears to be of vasomotor origin, which he thinks is often taken for phlebitis with thrombosis. The onset is acute with rather diffuse pain, most marked in limited areas; there is superficial tenderness, relieved by deep pressure, and swelling of the whole or part of the affected limb without œdema or pitting. If the whole limb is involved the contour is preserved. The swelling and pain are independent of posture, but the pain is markedly influenced by changes in temperature. There may be marked bruising after pressure on the affected area, and dusky lines may form along areas where there has been slight pressure from clothes. Often the swelling is fairly well limited to areas supplied by certain cutaneous nerves, especially the internal and middle cutaneous, the saphenous plexus, the external cutaneous, and the musculo-cutaneous of the thigh. The reflexes are normal. Possibly the condition is similar to one described by Northrup[2] in 1896 as phlebitis migrans, although this observer believed the condition due to a periphlebitic lymphangitis.

Phleboliths in the superficial veins of the legs may be mistaken for the subcutaneous fibroid nodules of rheumatism and chorea, as in the patient whose case is recorded by Rolleston.[3]

[1] *British Medical Journal*, 1904, ii, 1553.
[2] *Transactions of the Association of American Physicians*, 1896.
[3] *Lancet*, 1906, i, 29.

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Thrombosis of the Superior Vena Cava.[1]—Thrombi in the superior vena cava are rarely autochthonous, although in 10 of the 29 cases of obliteration of the vein collected by Hume the process originated in disease of the vessel wall. Heickmann and Duchek have each recorded cases in which the thrombus was propagated from peripheral vessels, but generally the process, if originating within the vessel, is a simple phlebitis. The majority of instances are associated with compression of the vein by tumors, aneurism, or chronic inflammatory disease involving the vessel in cicatricial tissue. The symptoms depend on the degree of establishment of the collateral circulation and in most instances the immediate consequences of the thrombosis are so severe that death rapidly ensues. Osler states that the clinical picture in individuals who survive and establish a collateral circulation appears under one of two types. In one class of cases the patient has for years complete compensation with good health followed by the sudden appearance of urgent symptoms, usually attacks of dyspnœa with recurrent effusion into the pleural cavities. In the second group of patients symptoms of obstruction of the venous circulation are constantly present. In Osler's first case there was pain in the chest with swelling of the face on exertion, cough, and cyanosis. The patient died of tuberculosis. Dilatation of the superficial veins is a prominent feature in these cases. The veins concerned in the collateral circulation vary according to the situation of the thrombus. If this occurs distal to the azygos vein the collateral circulation takes place, according to Forel, mainly through this vessel. In Osler's case there was marked enlargement of the lateral thoracic veins and the superficial epigastric veins which carried the blood from the subclavian into the common iliacs.

Thrombosis of the Inferior Vena Cava.—In the inferior as in the superior vena cava autochthonous thrombi are rare, and thrombosis usually results from propagation of thrombi from affluents, or from compression of the vein by neoplasms, aneurism, or the products of inflammation. Instances are on record of thrombosis of the inferior vena cava from compression at the point of passage through the diaphragm as the result of sagging of this muscle from the weight of a left-sided pleural exudate. Disease of the vessel wall, either simple phlebitis or new-growth, may cause thrombosis of the vena cava, and occasional instances after the infectious diseases have been noted. Compression by the enlarged head of the pancreas is a rare cause.

Thrombosis of the inferior vena cava, even when complete, may fail to produce symptoms, but this usually occurs only in old or prostrated individuals in the terminal stages of some debilitating disease with great enfeeblement of the circulation. Usually there is a well-marked œdema of the lower extremities, especially of the back, without ascites. The œdema may be unilateral, as has been noted by Schlesinger. This may be due to congenital duplication of the vena cava or some peculiarity in the communication between the veins of the upper and one lower extremity. It may occur because the thrombus in the vena cava is propagated from the iliac on one side, is parietal, and does not occlude the other iliac. Sometimes the œdema does not occur on one side because an old thrombus of one iliac vein has led to the formation of a collateral circulation. Involvement of the renal veins may cause a diminution in the secretion of urine, with albuminuria and hæmaturia, but, as Welch points out, these symptoms do not always appear.

[1] Osler, *Johns Hopkins Hospital Bulletin*, July, 1903.

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Involvement of the hepatic veins may lead to portal obstruction with enlargement of the liver, spleen tumor, and ascites. In patients who survive, an extensive collateral circulation is established. This may involve only the deeper veins, rendering diagnosis impossible, or more commonly the superficial veins of the groins and trunk take part. In cases with the superficial compensatory circulation the communication between the affluents of the inferior vena cava and the superior vena cava is carried on by the epigastric veins, the circumflex iliac veins, the long thoracic veins, the internal mammary veins, the intercostal veins, the external pudic vein, and the lumbo-vertebral anastomotic trunk of Braune. The deep anastomosis is carried on by the azygos and hemiazygos and the lumbar veins.

Thrombosis of the Renal Vessels.—Thrombosis of the renal artery will be considered with embolism, as the results are the same. Thrombosis of the renal veins is not infrequent and may be autochthonous, then usually associated with renal disease or debilitating conditions, or may be due to the extension of a thrombus from the inferior vena cava.

There is good evidence that in many instances thrombosis of the renal vein is not followed by marked symptoms. Welch states that it is the exception for a patient to present symptoms referable to the lesion. This lack of symptoms is most likely to be present when the thrombus forms gradually, as there are abundant anastomotic channels and a collateral circulation is rapidly established. In some patients thrombosis of the renal veins is followed by symptoms so definite that a diagnosis may be made without difficulty.[1] Briefly stated, the more important *symptoms* are pain in the region of the kidney, marked albuminuria, usually accompanied by hæmaturia and decreased amount of urine with a high specific gravity, and an enlarged, tender, palpable kidney. The pain may be very severe and may persist for weeks. Long after its disappearance the kidney may still be tender on palpation. The increase in size of the kidney may be very considerable, and it may be a simple matter to palpate it. The albuminuria is the most constant urinary change, and the amount of albumin may reach as high as fourteen pro mille by Esbach's albuminimeter. In patients who recover, albumin may still be present after a period of two or three months. Hæmaturia is not constant and is said by Hutinel to be much less liable to occur in children than in adults. It may be marked enough to be evident on examination of the urine with the naked eye. It persists a much shorter time than the albuminuria, in patients who recover usually disappearing in a week or two. Fever and the accompanying constitutional symptoms occur in connection with thrombosis of the renal veins in some instances. Bilateral thrombosis of the renal veins leads to anuria followed by death.

Thrombosis and Embolism of the Mesenteric Vessels.—Thrombosis of the mesenteric veins may either be secondary to portal thrombosis or may originate as a primary process in the branches of the veins. The primary form may be due to local or to general causes. The local causes take the form of inflammatory lesions of the intestinal wall, such as ulcers, or occur as enlarged mesenteric glands or pancreatic or gastric tumors causing thrombosis from compression. Occasionally local disease of the vessel wall, either simple phlebitis or luetic inflammation, is present. Of the general causes the infections, and especially typhoid fever and the various forms of

[1] Reese, *Deutsch. Arch. f. klin. Med.*, 1903, lxxviii.

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sepsis, must be mentioned. Thrombosis of the mesenteric veins not infrequently follows embolism of the arteries.

The *symptoms* of thrombosis of the mesenteric veins are essentially the same as those following embolism of the mesenteric arteries except that they are, if anything, more severe. In 5 out of the 157 cases collected by Jackson, Porter, and Quinby,[1] there were no symptoms referable to the abdomen. The most prominent symptoms in the average case are pain, nausea and vomiting, either diarrhœa or constipation, or both at different stages, abdominal tenderness, and signs of intestinal obstruction. Abdominal pain is present in the great majority of instances, and in over one-half of the patients is general in character. Localized pain when present is most common in the upper abdominal zones, either in the epigastrium or about the umbilicus. Radiation of the pain is fairly common, but there is no particular distribution which is characteristic. The onset of the symptoms is usually sudden, and there is often a constant dull ache with exacerbations of severe colic. The cause of the pain is thought to be the contraction of the intestinal wall, and its spasmodic character makes it analogous to the pain of angina pectoris or to attacks of intestinal colic from abdominal arteriosclerosis (angina abdominis). Nausea and vomiting are not necessarily present, and are more apt to be severe when the thrombosis occurs suddenly. The character of the vomitus depends on the severity and duration of the case, normal stomach contents being vomited early; later bile, fæcal material, or even pure blood. Diarrhœa is present in only 50 per cent. of the patients, and in 41 per cent. blood occurs in the stools at one time or another. The diarrhœa is preceded or succeeded by obstipation in a small percentage of patients. Obstipation alone occurred in 22 per cent. of the cases collected by Jackson, Porter, and Quinby. It is at times followed by diarrhœa, usually with bloody passages. Abdominal tenderness occurs in 70 per cent. of the patients, and in a large majority is, like pain, generalized. When localized it is most likely to occur about the umbilicus, in the cæcal region, or in the epigastrium. Distention is a late symptom and is practically always generalized. Leukocytosis and idiophilia were present in the Boston cases. The temperature varies; it may fall below normal, but not infrequently fever is present. Rare signs in thrombosis of the mesenteric veins are glycosuria and purpura.

The *diagnosis* of thrombosis of the mesenteric veins is usually difficult, inasmuch as in but few cases the majority of the symptoms are present. In a large number of cases the diagnosis of intestinal obstruction is made. The most characteristic signs are stated to be the sudden onset of colicky abdominal pains with a fall in the temperature and passage of blood-stained stools, and later symptoms of intestinal obstruction with distention of the abdomen and perhaps some ascites. Thrombosis of the mesenteric veins is not infrequently associated with thrombi elsewhere in the body, and may be directly secondary to portal thrombosis. The presence of such thrombi elsewhere or of symptoms referable to thrombi should make the diagnosis more simple. Aside from intestinal obstruction, the condition may be confounded, on account of the vomiting and passage of blood, with gastric or duodenal ulcer or with disease of the heart and liver, accompanied by passive

[1] Jackson, Porter, and Quinby, *Journal of the American Medical Association*, vol. xliii, No. 3.

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congestion in the abdominal organs. Differential diagnosis in these cases must rest upon the presence of other signs of these diseases. Patients in whom purpura is present in association with thrombosis of the mesenteric veins might be confused with instances of abdominal crises in connection with purpuric skin eruptions of the erythema group.

Thrombosis of the Portal Vein.—Thrombosis of the portal vein may result from disease in the vein itself, or much more commonly from pathological processes which cause compression of the vessel. In the vessel wall a sclerotic process comparable to arteriosclerosis has been occasionally described, but is quite rare. Usually portal thrombi not due to external pressure are of the propagated variety, are often although not necessarily septic, and are commonly associated with intra-abdominal inflammatory processes, especially appendicitis. Thrombosis from pressure may occur in connection with neoplasms of the head of the pancreas, the stomach, the omentum, or the lymph nodes in the hilum of the liver. Another group is associated with compression by cicatricial tissue either within the liver, as in cases of cirrhosis, or external to that organ, but surrounding the portal trunk. In the latter instance the scar tissue results from a localized peritonitis which may be due to gallstones, gastric or duodenal ulcer, or tuberculosis. Gallstones themselves have occasionally been situated so as to compress the portal vein and lead to thrombosis. A certain number of instances of portal thrombosis without apparent cause have been recorded, the so-called idiopathic portal thrombosis, but Ponfick and others think that these are instances of traumatic portal thrombosis such as have been recently described by Heller and Wilke.[1] In some instances the evidence of the relation to trauma is plain, in others not very satisfactory.

The *symptoms* of pylethrombosis are very different in septic and non-septic cases. Septic or suppurative pylephlebitis results in the formation of multiple abscesses in the liver, and the outcome is usually a rapid and fatal termination.

Appendicitis is so frequently the exciting cause of this form of portal thrombosis that the French school speak of it as "le foie appendiculaire."[2] The clinical picture in these patients is that of sepsis with local symptoms pointing to the liver. The onset is often sudden, with a violent chill, high fever and profuse sweating. The fever persists during the course of the disease, but is usually marked by exacerbations, often with chills, which may occur daily at about the same period, or may be more frequent and irregular. Quite early, as a rule, gastro-intestinal symptoms appear, nausea and vomiting with perhaps diarrhœa, which according to Dieulafoy may be paroxysmal. Constipation may, however, be present throughout. Jaundice and tenderness in the region of the liver are usually prominent signs, and as the disease progresses the liver may reach twice its normal size. The icterus varies in intensity, and may appear early in the disease or not until late. The patients finally pass into a typhoid state and die in collapse or may succumb with the symptoms of cholæmia.

The form of portal thrombosis associated with simple pylephlebitis gives rise, in the majority of instances, to a clinical picture resembling that of atrophic cirrhosis of the liver. In some patients, as in the remarkable one

[1] *Pfortavenenthrombose und Trauma*, Inaug. Diss., Kiel, 1903.
[2] Dieulafoy, *Clinique médicale de l'Hôtel Dieu*, 1897–98.

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reported by Saxer,[1] most extensive thrombosis of the main branches of the portal vein may occur without characteristic symptoms. Usually enlargement of the spleen, ascites which recurs rapidly after tapping, and the formation of a collateral circulation are prominent features. The collateral circulation may involve the superficial veins of the abdomen and lower chest, and is then plainly apparent, or it may occur through the left coronary vein of the stomach, the œsophageal veins, the intercostal veins, and the azygos veins. In the latter instance large varices may form beneath the mucous membrane of the stomach or lower end of the œsophagus, and such patients are apt to suffer from sudden and severe hæmatemesis or melæna. The ascites which is so prominent a feature in some patients may be lacking in those in whom such hemorrhages occur. On the other hand, patients with well-marked ascites do not usually have the gastric and intestinal hemorrhages. The minor manifestations of portal obstruction, anorexia, nausea, and intestinal disturbances, may be present, especially in long-standing cases. Jaundice does not occur unless complications are present. A few patients recover as the result of the formation of a fully compensating collateral circulation, but as a rule a fatal termination is to be expected either from severe gastric or intestinal hemorrhage, from gradually increasing asthenia, or from extension of the thrombosis or involvement of the mesenteric vessels and infarction of the intestine. When the process comes on gradually and gives rise to a picture of chronic portal obstruction, it may be impossible to differentiate it from atrophic cirrhosis of the liver, especially as this organ is often, although not invariably, decreased in size in cases of portal thrombosis. In the acute cases the rapid onset in an individual with a previously clean record, the absence of an alcoholic history, the absence of decrease in size of the liver, or even the enlargement of this organ, the early appearance of ascites and its rapid recurrence after tapping, or the presence of severe gastric or intestinal hemorrhages—all suggest a portal thrombosis rather than cirrhosis.

Thrombosis of the Hepatic Veins.[2]—Attention has been called in recent years, especially by Chiari and his pupils, to a form of thrombophlebitis of the hepatic veins which has not as yet been described in this country, but which is probably not very uncommon. It is overlooked no doubt because the symptoms and the gross pathology are essentially those of hepatic cirrhosis. Postmortem examination shows in most cases an obliterating endophlebitis of the hepatic veins, usually associated with thrombosis. Not infrequently thrombi are also present in the branches of the portal vein. The gross and microscopic picture, aside from the changes in the veins, closely resembles that of atrophic cirrhosis.

The disease attacks both sexes alike, usually during young adult life, and seems at times to develop upon a luetic basis. The *symptoms* as a rule appear gradually, although in rare cases an acute onset with death in less than two weeks has been noted. Usually a sense of pain and discomfort in the hepatic region or the upper abdomen is the first thing noted. Later symptoms suggestive of atrophic cirrhosis occur, the abdomen gradually enlarges, ascites develops, and gastro-intestinal disturbances may appear. The signs

[1] *Cent. f. Allgem. Path.*, 1902, vol. xiii, Nr. 15.

[2] Hess, *American Journal of the Medical Sciences*, 1905, vol. cxxx; Umbreit, *Virchow's Archiv*, 1906, vol. clxxxiii.

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of a compensatory circulation may be apparent in the form of a caput medusæ. Hæmatemesis and melæna occur in rare instances, much less commonly than in portal thrombosis. Hæmaturia has been occasionally noted. Physical examination shows the presence of fluid in the abdominal cavity, which, if withdrawn, rapidly re-accumulates. It usually has the characteristics of a simple transudate, but is occasionally hemorrhagic. The liver is in the early stages enlarged, smooth, and firm; later it becomes contracted and more or less nodular. Jaundice is generally absent. The spleen is enlarged, hard, and easily palpable. In the final stages of the disease general anasarca may appear. There is as a rule no fever, and the urine is negative. In most patients the course of the disease is shorter than that of an ordinary cirrhosis, the average duration after the onset of symptoms being about six months.

Hess states that no case of this disease has been diagnosed during life, most patients having been considered to be suffering from cirrhosis of the liver. Two acute cases with marked gastro-intestinal symptoms and prostration were diagnosed as poisoning in one instance and intestinal obstruction in the other. According to Hess, the main points in distinguishing hepatic thrombophlebitis from cirrhosis are its occurrence in younger individuals, the absence of the cause of cirrhosis, the presence of pain in the hepatic region, the rapid development of ascites, and the frequency with which paracentesis is needed.

Thrombophlebitis of the Umbilical Veins.—The occurrence of infection of the umbilical veins in the newborn child is one of the most serious diseases of early life. The condition is often insidious in onset, for, as a rule, there are no marked local signs in the umbilical stump. In occasional complicated cases pus can be squeezed from the severed end of the vein, but this is exceptional. It is stated by some observers that the more severe the infection the less the likelihood of marked local symptoms. Usually the symptom which calls attention to the condition is a gradually intensifying jaundice, which is often accompanied by symptoms of sepsis. Later hemorrhages may occur, most often from the stump of the umbilical cord. Fever may be marked. There may be inflammation of the serous membranes, pericarditis especially, and occasionally gangrene of the umbilical stump, or erysipelas of the skin surrounding it. The inflammation usually extends to the veins of the liver and causes a diffuse hepatitis or multiple abscesses of the liver. The prognosis is very grave, much more so than that of the more frequent umbilical arteritis.

Thrombosis of the Vessels of the Spleen.—Thrombosis of the main trunk of the splenic artery occurs very rarely, although this vessel is frequently the seat of arteriosclerosis. Thrombi in the smaller arterial branches give rise to the same symptoms as emboli, and will be considered under that head. Thrombosis of the main trunk of the splenic vein is rare. It may occur as a terminal process in connection with sclerosis of the vessel accompanying splenic anæmia, as reported by Dock and Warthin.[1] Thrombi in the smaller branches of the vein occasionally cause infarcts. Septic thrombosis of the splenic vein may occur in connection with infectious processes in the pancreas from the contiguity of the vessel to that organ. The vein may be thrombosed as a result of typhoid fever. The condition is of pathological rather than clinical interest.

[1] *Transactions of the Association of American Physicians*, 1903.

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Thrombosis of the Pulmonary Vessels.—Thrombi in the pulmonary veins are common enough in the areas involved in inflammatory conditions of the lung, infarcts and tumors, and in emphysema. They occasionally give rise to emboli in the systemic circulation. Thrombi in the pulmonary arteries, even when they cause blocking of medium-sized branches, often, as Newton Pitt has pointed out, give rise to no marked changes in the lung. When changes occur they resemble both clinically and pathologically those due to embolism, and will be considered under that head. Box[1] has recently suggested that in many instances emboli of the medium-sized and smaller pulmonary arteries are due to the detachment of primary parietal thrombi originating in the large branches, which they do not completely occlude. He believes that the presence of such non-occluding thrombi of the main branches of the pulmonary artery can be detected clinically, or at least suspected, and that precautions can be taken which may prevent dislodgement in some patients, avoiding fatal embolism. The premonitory signs which he considers of value are a harsh, systolic basic murmur in the pulmonary area (this is not invariably present), an undue acceleration of the pulse, which may occur a day or two before the fatal embolism, and cyanosis, usually slight, with dyspnœa.

The occurrence of *arterial thrombosis* has been discussed to some extent under the heading of various diseases concerned in its etiology. The symptoms so closely duplicate those of embolism that the two conditions will be considered together.

Capillary Thrombosis.—Capillary thrombosis, as already mentioned, is of pathological rather than clinical interest. The possible relationship of capillary thrombi in the kidney glomeruli to disturbances in the secretion of urine, as suggested by Welch, seems worthy of further investigation. Herzog's work on the plague indicates that such thrombi may be numerous enough in some cases of this disease to cause urinary changes, but the clinical histories of the patients from whom he obtained his material are unfortunately lacking. The relation of capillary thrombi to gastric hemorrhage and to ulcer and the so-called gastric erosions, especially in connection with postoperative hæmatemesis, has been suggested by von Eiselberg and others, but needs further confirmation.

Cardiac Thrombosis.—The diagnosis of the ordinary parietal cardiac thrombi from any direct effect they may produce upon the heart itself is generally considered to be impossible. It is stated by Gerhardt that thrombosed auricular appendages may press on the pulmonary artery and cause a systolic murmur in the region of this vessel, but Huchard says this is exceedingly unusual. The presence of parietal cardiac thrombi may be suspected when, during failure in compensation without distinct evidences of valvular endocarditis, symptoms of embolism occur in organs supplied by the systemic circulation. Pedunculated thrombi and ball thrombi may be associated with sudden death with symptoms of syncope. Whether this is due to the blocking of the auriculo-ventricular opening by the thrombus is still a matter of discussion. In other instances ball thrombi are believed to give rise to symptoms which permit of a possible diagnosis, although, as Babcock states, it is doubtful if a correct diagnosis has ever been made during life. The symptoms are essentially those of an exaggerated mitral stenosis, marked

[1] *Transactions of the Clinical Society of London*, 1906, vol. xxxix.

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dyspnœa, cough, an unusually feeble pulse, and evidences of venous engorgement out of proportion to the degree which is usual in uncomplicated mitral stenosis. Localized gangrene of the foot, which von Ziemssen described in his patients and considered almost pathognomonic, is not necessarily present. The physical signs are those of mitral stenosis, although the presystolic murmur is said to be absent in some instances, and, when present, to show a marked tendency to intermittency. As diagnostic points, von Ziemssen emphasizes, the physical signs of mitral stenosis, the occurrence of the ordinary clinical signs of this lesion in an exaggerated form, especially a very small and feeble pulse, and circumscribed gangrene of the foot.

Sequelæ of Thrombosis.—Aside from those instances in which the symptoms essentially represent the sequelæ of thrombosis, as in thrombosis of the portal or hepatic veins, the remote results of thrombosis of the vessels of the internal organs are as a rule unrecognizable, for if the changes in the affected organ are not sufficient to cause death they are subsequently compensated for by the unaffected portions of the viscus, or, in cases of paired organs, by the uninvolved one. Changes in the central nervous system due to thrombosis are not, of course, followed by recovery of function if the lesion is at all extensive. Certain remote effects of peripheral thrombosis, and especially of peripheral venous thrombosis, need brief discussion. Of peripheral arterial thrombosis it need only be stated that the sequelæ are the same as of arterial embolism.

The important sequelæ of peripheral venous thrombosis may be considered under two heads: first, the occurrence of secondary embolism, and, second, the probable local effects. The factors which influence secondary embolism have already been briefly discussed in connection with the disease associations of thrombosis. As a general rule septic thrombi are more apt to give rise to secondary emboli than bland ones, and certain forms of thrombosis are commonly associated with embolism, whilst in others this sequel is almost unheard of. Thus puerperal thrombosis and thrombosis chlorotica commonly result in secondary embolism, whilst syphilitic thrombosis almost never does so. Typhoid thrombosis is one of the forms in which secondary embolism is rather unusual, as it is in idiopathic recurrent thrombosis. There is, too, apparently some difference in the likelihood of embolism according to the vein affected. Haward's table shows secondary embolism most frequently after thrombosis involving the iliac veins, next in frequency after saphenous and femoral thrombosis, and only occasionally after thrombosis of the veins of the leg or of the viscera. The fact that the danger of embolism can be greatly increased by sudden movements on the part of the patient or by undue manipulation of the affected vein by the physician should always be kept in mind.

Of the local complications of peripheral venous thrombosis, the perivascular suppuration has already been mentioned. Much more important are the more or less disabling sequelæ which may occur when a large vessel like the femoral is permanently plugged. In patients who have suffered from such a lesion there may be present for years, even during the remainder of life, certain annoying symptoms. The most common of these are a feeling of heaviness and clumsiness in the limb, œdema, especially at night and after exercise, stiffness of the joints, and impairment of the circulation with coldness of the member. Changes in the muscle of the limb, usually in the form of atrophy, are frequent; rarely a well-marked hypertrophy of the muscles

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results. To these symptoms must be added pain, which may be present along the course of the thrombosed vessel or may be more widespread, and is especially apt to invade the territory of the sciatic. Usually slight, the pain may be intense, neuralgic in character, and quite intractable. At night or after exertion distressing cramps in the muscles may be present.

Diagnosis and Prognosis.—The diagnosis and prognosis of thrombosis varies so much according to the disease associations and the vein affected that a general discussion of the subject is impracticable. The main points bearing on both diagnosis and prognosis will be found in the discussion of the disease associations and of the symptomatology of thrombosis of different vessels.

Treatment.—The treatment of thrombosis practically resolves itself into the treatment of peripheral thrombosis and of one or two forms of visceral thrombosis in which operative interference may with propriety be essayed.

The prophylaxis of thrombosis has not as yet been seriously considered, and it is hard to see how this can be done unless we are to regard all patients suffering from certain diseases as possible candidates for this complication. We have as yet no way of telling what patients are likely to develop thrombosis, nor are we sure that the underlying factors are the same in all instances. In one disease at least, typhoid fever, prophylactic measures have been suggested. Wright and Knapp[1] consider that the thrombosis which is so common after this disease is due to the excess of lime salts in the blood, this in turn depending upon the milk diet which is so commonly in use in this disease. They suggest that a partial decalcification of the milk by the addition of 0.25 to 0.5 per cent. of citrate of soda might be of value as a prophylactic measure. This should of course be done only after the danger of intestinal hemorrhage is past. In view of the frequency with which a milk diet is used in other febrile diseases, this suggestion might be borne in mind in the dieting of patients with any disease likely to be complicated with thrombosis.

The immediate treatment of patients with peripheral thrombosis consists first of all in the immobilization of the limb in order to minimize the danger of embolism, and secondly in such symptomatic treatment as is demanded. The limb must be placed in a comfortable position and the immobility must be absolute, the necessity for this being strongly impressed both upon the patient and the attendants. So far as the patient is concerned, he must not only be warned against sudden movements, but also against straining at stool and excessive coughing, and laxatives or pulmonary sedatives may be administered to aid him in doing this if necessary. Mechanical methods must be employed to fix the limb, and at the same time pressure in the immediate neighborhood of the thrombosed vein must be avoided. This may be done in the case of femoral thrombosis by the application of a well-fitting, properly padded splint reaching the whole length of the limb, or, after wrapping the leg in cotton wadding, by a series of broad, strong strips of bandage passing over the anterior surface and fastened to the mattress on each side by safety pins. If the latter method is used, the pelvis should also be fixed by bands and the foot held in an upright position at right angles to the leg. The use of bandage strips has the advantage over the use of the splint of allowing easy access to the limb with a minimum of manipulation

[1] *Lancet*, December 6, 1902.

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The only subjective symptoms likely to demand treatment at this time is the pain, which may be intense. Morphine hypodermically is the only remedy of value in severe cases, but its use is seldom necessary after two or three days. This general treatment may be supplemented by the local application of an ice-bag or of hot fomentations. Belladonna ointment applied along the course of the vein or 30 per cent. ichthyol in lanolin have been recommended. The application of cold compresses moistened with normal saline solution for two or three hours daily during the second week is also recommended, as are applications of the old lead and opium lotion. All local medication should be applied with the greatest care.

In the treatment of peripheral thrombosis after the acute symptoms have subsided the important question to be decided upon is how long absolute immobility is to be maintained. The French school especially, who have given much thought to the matter, insist that many of the ordinary local sequelæ of thrombosis may be avoided by beginning passive motion and massage early. The three indications for beginning active treatment are, according to Quénu,[1] absence of fever for three weeks, disappearance of local tenderness over the affected vessel, and progressive decrease in the œdema. The plan outlined by this writer is as follows: During the first week that movement is permissible, only passive motion is allowed, consisting of gentle superficial rubbing and gentle movement of the different joints of the affected limb. During the second week massage of the muscles, avoiding the region of the vessel, and more marked passive motion of the joints are employed, although marked flexion of the joints in the neighborhood of the thrombus should be guarded against. During the third week the restraining bands or splint may be gradually removed, so that at the end of this week all mechanical restraint has been removed and the patient is allowed to move the limb gently in bed. During the fourth week the patient may be allowed to increase the movements of the limb in bed, and finally to get up. The limb should at first be supported by a bandage, preferably one of some light elastic tissue, as the heavy stockings used in patients with varicose veins may hinder the formation of the collateral circulation. The use of some support, preferably a cane, will be necessary when the patient begins to walk, but may be discarded as power and confidence are regained. In patients in whom œdema and pain persist for a long time after convalescence, these symptoms may require special treatment. For the œdema the use of massage and electricity and the wearing of a light supporting bandage is necessary. For the pain the application of tincture of iodine over the painful points, local warm douches or warm baths, and the use of electricity are of value. The latter remedy may be applied in the form of the high-frequency current, or if pain is not very marked the constant current in doses of from 25 to 50 ma. may be passed through the limb for some fifteen or twenty minutes daily. Faradization applied so as to produce intermittent contractions of the muscles over a period of ten to fifteen minutes daily may be of use in some patients in whom the pain is slight. According to Cleaves, electrical treatment should be begun during the latter part of the acute stage of thrombosis. The continuous current is first used in doses not to exceed 5 ma. for a few minutes daily. The current must have an unvarying rate of change, and must be capable of producing long, wave-like, undulatory

[1] *La semaine médicale*, July 26, 1905.

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muscular contractions. In chronic cases where a whole leg or arm is stiff and œdematous, the indifferent contact is best made at first by placing the foot or hand in a 1 per cent. saline bath at 100° F. charged from the indifferent pole. The active contact is made by a hand electrode which is passed over the affected limb. After a week or two the indifferent contact may be placed over the lumbar enlargement so as to apply the stimulant directly through the nerve supply. Treatment should be applied at first daily for ten minutes in doses of 8 ma., gradually increased as the treatment progresses to 20 ma. The treatments may be reduced in number after the first two weeks, first to two or three a week and later to weekly treatments. Usually from one and a half to three months' treatment is necessary. The sinusoidal current may be used as an adjunct during the later stages of the treatment. Internal medication is of no value except in special forms such as luetic thrombophlebitis.

The surgical treatment of peripheral thrombosis has been suggested by Moullin in patients in whom the superficial veins are involved, and by Briggs in idiopathic recurrent thrombophlebitis. Moullin[1] has been in the habit of excising the whole thrombosed vessel in such cases, and claims that it shortens the period of illness and removes the risks of secondary embolism, deep thrombosis from extension, and recurrence in the same vessel. There seems no reason why his method should not be more extensively employed in selected cases.

Treatment of thrombosis of visceral vessels must in most instances be purely symptomatic. The chances of detachment of emboli from thrombi in visceral veins is slight; nevertheless, absolute rest in bed should be required where visceral thrombosis is suspected. In the case of mesenteric and portal thrombosis, there is hope that operation will save a small percentage of patients. In mesenteric thrombosis and embolism the mortality after operation is at present 92 per cent. (Jackson, Porter, and Quinby). Without operation, however, the patient is almost certainly doomed, and with increased skill in diagnosis and improvement in technique the percentage of successes can doubtless be increased. The operation chosen should be one which can be quickly performed with a minimum chance of shock. The procedure recommended by Jackson, Porter, and Quinby, *i. e.*, bringing the involved intestine into the wound, resecting with liberal margins, and fixing the open edges in the wound, seems most logical. It is possible that the Talma operation or some modification of it might be of value in thrombosis of the portal or hepatic veins provided a diagnosis could be made early enough.

EMBOLISM.

The term embolism is applied to the obstruction of an artery, vein, or lymphatic from the lodgement in its lumen of undissolved foreign matter carried there by the circulation. The mass producing the obstruction is spoken of as an embolus.

Etiology.—A discussion of the etiology of embolism resolves itself into a consideration of the sources and incidentally the varieties of emboli. It

[1] *British Medical Journal*, 1904, ii, 1688.

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may be well to first briefly consider in a general way the phenomena of embolism.

Under ordinary circumstances emboli are composed of detached particles of thrombi, and the seat of their lodgement depends on their point of origin. They may be arrested in the arteries of the systemic circulation, in the pulmonary artery or its branches, or in the portal vein, which has a distribution similar to that of an artery. Usually emboli which lodge in the systemic arteries or their branches originate in the left side of the heart, in the main arterial trunks, or rarely in the branches of the pulmonary veins. Under some circumstances it is believed that minute systemic emboli may originate in the venous system, passing through the large pulmonary capillaries. Emboli which lodge in the pulmonary artery or its branches usually originate either in the systemic veins or in the right side of the heart. There is reason to believe that occasionally they originate from non-occluding parietal thrombi of the main branches of the pulmonary artery itself. Emboli which lodge in the portal vein or its branches originate in the affluents of that vessel, viz., the pyloric, gastric, cystic, superior mesenteric, or the splenic veins or their branches.

From the above statements it will be seen that particles free in the circulation naturally tend to move onward so long as the vessels in which they travel increase in caliber, and are finally stopped when they reach a branch of a vessel of diminishing caliber through which they cannot be forced by the blood or lymph stream. Ordinarily emboli lodge only in arteries, or in vessels like the portal vein which have peculiarities of distribution like an artery. Ordinarily, too, emboli in the systemic circulation originate only on the left side of the heart, in the larger arteries, or in the pulmonary veins. There are two exceptions to these general rules which must be briefly considered.

Venous emboli have been noted occasionally, usually, although not always, in veins without valves, and are most common in the subclavian vein, the innominate vein, the axillary vein, the pulmonary veins, the venæ cavæ, the hepatic veins, the cardiac coronary veins, the cerebral sinuses, the mesenteric veins, and the veins of the pampiniform plexus. They are spoken of as "retrograde" emboli, as they are due to the transportation of a thrombus formed elsewhere in the venous system in a direction opposite to the usual course of the blood stream. The cause of these retrograde emboli is still under discussion, the favored view being that they result from a backward flow of the venous current due to the sudden temporary stoppage of the return flow of the blood to the heart.

The second exception to the general rules covering the sources of emboli is the so-called "*paradoxical*" embolus, also spoken of as the "*crossed*" embolus. This name is applied to an embolus lodging in an artery of the systemic circulation which originated in the systemic veins or the right side of the heart and reached its place of lodgement by passing through an open foramen ovale. How frequently this form of embolism occurs is uncertain. Its occurrence has been absolutely demonstrated in one or two instances by finding the plug engaged in the foramen ovale. It is probable that the passage of large emboli by this route is very unusual; even small ones would have difficulty in passing through the ordinary patent foramen ovale, for although the opening is present in probably over 30 per cent. of individuals, it is nearly always protected by a membranous flap, and under the usual

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pressure conditions in the cardiac cavities it is hard to see how emboli could pass through it. It is conceivable, however, that with a marked increase in the intracardiac pressure in the right auricle associated with diminished pressure in the left auricle the passage of small particles through the foramen ovale might not be difficult.

Origin of Emboli.—All emboli are not composed of detached particles of thrombi, for while by far the largest number are of this nature, various substances may gain entrance to the circulation and obstruct the bloodvessels. These may be divided into two great groups according to their origin: endogenous emboli, which originate within the heart or bloodvessels, and exogenous emboli, which have their origin outside of the circulation, but gain entrance to it in one way or another. Both groups may again be subdivided, according to their nature, into bland or inert emboli, and active emboli, the former being harmless aside from their purely mechanical action, the latter being either infective or composed or living cells or of parasites.

The bland endogenous emboli are usually broken-off particles of bland thrombi, but may consist of detached fragments of calcareous material originating from sclerotic patches in the valves or the vessels, of particles of detritus from atheromatous abscesses or ulcers, of pieces of clot from the interior of aneurisms or from the heart valves, or of material originating from the destruction of blood corpuscles or of blood parasites such as the malarial plasmodium. In the latter instance pigment emboli occur.

The exogenous bland emboli may be of a solid, a liquid, or a gaseous nature. Solid emboli originating outside of the vascular system are very rare unless we include solid particles introduced into the blood stream for experimental purposes. There is at least one remarkable case on record in which a revolver bullet entered the circulation and acted as an embolus. Of the liquid emboli, the most common are fat emboli, usually seen after fractures, but also observed after concussion of the body, inflammation of the subcutaneous fatty tissue, and sometimes after infections with fatty degeneration of the internal organs. Certain semiliquid or liquid substances introduced subcutaneously for medicinal or cosmetic purposes, such as oil, mercurial preparations, and paraffin, may also give rise to emboli. Gaseous emboli may be due to the introduction of atmospheric air in the veins during operations or after labor, but in many instances so-called air emboli are due, as Welch has shown, to the production of gases within the circulation by gas-forming bacteria, and especially by the *Bacillus aërogenes capsulatus*.

The active, or, as the French call them, animated emboli, like the bland ones, may originate either within or without the circulation. In the first group may be mentioned emboli of leukocytes and emboli originating from infective thrombi, although in the latter instance the infective element really originated outside of the circulation. In the second group emboli composed of body cells of various kinds, notably of cells from the bone-marrow, placenta, or liver, are not infrequent, and are sometimes spoken of as autositic emboli. Parasitic emboli are, of course, frequent in bacterial infections, especially in anthrax, glanders, tuberculosis, leprosy, and malignant œdema. The higher forms of vegetable parasites, the moulds and actinomyces, for example, may also form emboli. Finally, animal parasites, as the larvæ or ova of filariæ, trichinæ, strongyloides, flukes, and tæniæ, may obtain entrance to the circulation and produce embolism.

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Special Pathology.—Site of Deposit of Emboli.—It is not to be assumed that all particles free in the circulation succeed in lodging in a vessel. Rarely the particles originating in the systemic or pulmonary veins become entangled in the meshwork formed by the chordæ tendineæ or the columnæ carneæ, and never get beyond the cavities of the heart. Still more rarely large emboli may lodge in the auriculo-ventricular orifices, obstructing them and causing sudden death. It is also to be borne in mind that the caliber of the embolus is often much greater than that of the vessel it obstructs, either because a long, thin embolus becomes folded, thus increasing its diameter, or because an embolus by lodging crosswise on the partition at the point of division of the vessel (riding embolus) interferes with the circulation of two branches at once.

Pathological studies seem to show that emboli free in the blood stream do not lodge indiscriminately in any vessel, but that the vessels of certain organs are especially prone to be plugged. The data bearing on this matter are, as Welch points out, subject to considerable error, for they are founded on the study of emboli which have caused distinct lesions, whereas it is well known that many emboli produce no appreciable gross lesions, and in the absence of these a complete search for them, even under the microscope, would resemble the hunt for the proverbial needle in the haystack. Welch believes that the systemic arteries going to the lower extremities receive more emboli than vessels elsewhere. In the case of infective emboli there is a tendency to occur in those places where the circulation is naturally slowest, as in the liver, and also to create lesions in some locus minoris resistentiæ. So far as bland emboli are concerned, various lists have been prepared giving their sites of predilection, but these frequently do not agree. According to Welch, the vessels most commonly affected are, in the order of frequency, the pulmonary, renal, splenic, cerebral, iliac, and arteries of the lower extremities, axillary and arteries of the upper extremities, cœliac axis and its hepatic and gastric branches, central artery of the retina, superior mesenteric, inferior mesenteric, abdominal aorta, and coronary of the heart. It is to be observed of the vessels in this list that the ones most frequently affected are either those in direct line of fire from the commonest origin of emboli, venous thrombi, or those supplying organs whose cells are most easily injured by disturbances in their blood supply. Certain purely mechanical factors concerning the emboli themselves, the course of the blood stream, and the size and arrangement of the vessels also play a part in determining the point of lodgement. The action of gravity, the weight and size of the embolic mass, and the degree of obliquity with which branches are given off from the main arterial trunk, are the most important of these factors. The presence of changes in the walls of the arteries, such as roughening from atheroma or narrowing from external pressure, also doubtless play a part in many instances.

Anatomical Characters.—The appearance of emboli varies with their character and age. Sometimes, especially when seen soon after their lodgement, they are easily distinguished from thrombi, but if they have been long in the vessel, so that a secondary thrombus has formed about them, the distinction may be impossible. The fresh embolus is distinguished from the thrombus by its shape, which is often more or less irregular, by its lack of adhesiveness or slight adhesiveness to the vessel wall, and by the fact that it may have the appearance of tissue from an old thrombus and that at some

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point on its surface there is often evidence that it has been detached from a larger mass. The secondary thrombus which usually forms about an embolus causes it to become adherent to the vessel wall, and it then on casual observation appears like an ordinary thrombus. Incision into such a plug may show that the central portion has a much older appearance than the periphery, and may even be calcified, but convincing evidence on this point is often lacking. The most important point in doubtful cases is the detection of a source for an embolus, and unless care is taken this can easily be overlooked. It is impossible in some instances, as in deep-seated thrombi in bones, to detect the primary thrombosis, but this is more often missed because certain veins which are commonly the seat of thrombi, such as the small veins of the prostate and the base of the bladder, and the veins of the broad ligament, are not carefully examined in the ordinary autopsy. The condition of the vessel and the clinical history must also be taken into account in reaching a conclusion, although it must not be forgotten that changes in the vessel wall may predispose to the lodgement of embolus as well as to thrombosis, and that the clinical history of a very sudden onset of symptoms, which is usually regarded as favoring embolism, is by no means uncommon in thrombosis.

Effect on the Tissues of the Lodgement of an Embolus.—In certain vessels supplying vital organs, such as the main branches of the pulmonary arteries or of the coronary arteries of the heart, the lodgement of an embolus is usually followed by sudden death. Aside from such special vessels, the changes produced by the lodgement of an embolus depend upon the character of the cells and the circulation of the affected tissue, and upon the character of the embolus. Bland emboli produce merely mechanical effects; active emboli produce in addition chemical and sometimes vital changes.

The effect of the lodgement of bland emboli in the vessels of certain organs and tissues with an extensive and freely anastomosing blood supply, and cells which bear well temporary interference with their nourishment, may be quite inappreciable. Thus emboli of the vessels of the liver, the thyroid, the bones, the urinary bladder, the female genital organs, and the more vascular portions of the skin, result as a rule in a temporary anæmia quickly followed by the formation of a collateral circulation. A complete discussion of the mechanism of the formation of such a circulation will be found in Welch's article in Allbutt's *System*.

Bland emboli in tissues whose circulation is anatomically terminal, or is insufficient to supply blood by collaterals to cells easily succumbing to the effects of anæmia, result in necrosis. The type of necrosis produced varies according to the character of the structure affected, and its relations to the surrounding tissue. If the part whose circulation is cut off is segregated from the rest of the tissues, as occurs after embolism of the main artery of an extremity, the resulting process is known as gangrene or mortification. If the affected tissue is a small segment of an organ, and is surrounded by normal tissue from which lymph can flow into it, the result will be either an area of softening, as occurs in the central nervous system, or, if large quantities of coagulable material are absorbed by the necrotic cells, coagulation necrosis in the form known as an infarct. In certain structures, as the kidney, spleen, brain, intestine and retina, infarction almost invariably takes place. In others, perhaps on account of individual peculiarities in the circulation, it does not always occur. Thus bland emboli in the lungs do not

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usually produce infarcts. Bland emboli of the larger cerebral arteries, on account of the circle of Willis, often produce but little effect. Embolism of the main vessels of the extremities, and even of the aorta itself, may not result in necrosis.

When infarctions occur their appearance is not always the same owing to individual peculiarities in the cells or tissues of certain organs. In general, infarcts have a conical shape with the base of the cone toward the periphery of the organ, this being due to the fact that they correspond to the distribution of the branches of the particular arterial trunk which has been plugged. Their consistency varies somewhat with the character of the organ, being not quite so firm in a loose-meshed organ with chances for expansion as in a compact one enclosed in an unyielding capsule. The main variation, however, lies in the color, which may be red (hemorrhagic) or white (anæmic). Some authors describe mixed infarcts, and in the kidney, where the distribution of the vessels in the medulla is different from that in the cortex, a white infarct with a red apex may occur if the infarcted area is partly included in the medullary zone. The factor which makes the difference between the red and the white infarct is the presence in the infarcted area of red blood corpuscles, and the character of the cells of the affected organ, or sometimes other peculiarities of structure, determine whether red blood cells shall be present in numbers. In the kidney soon after the blood supply is shut off from the affected part, the sensitive cells die and absorb serum from the small amount of blood carried in by the scant collaterals. As a result the cells swell rapidly, compress the cortical vessels, and prevent any marked influx of blood. We therefore get white infarcts in the kidney, although, as mentioned above, inasmuch as in the medulla the vessels are more numerous, better protected by intervening connective tissue, and not so subject to compression by the swollen cells, the portion of a kidney infarct lying in the medulla may contain a good many red corpuscles. Very much the same thing occurs in the brain, whose cells are even more sensitive to interference with their blood supply than those of the kidney. Here instead of a white infarct we get an area of white softening. In the spleen, on the other hand, the interference with the blood supply irritates the muscle fibers in the capsule and trabeculæ, and causes them to contract, forcing out the blood. After a certain period, perhaps some days, the muscle relaxes, but by this time changes in the walls of the vessels have occurred. They are no longer able to retain the blood, which escapes into the affected area and swamps it with serum and corpuscles, resulting in stasis and finally necrosis. In the lung the element of infection comes into play, the bacterial toxins producing changes in the vessel walls which allow the passage of the blood into the alveoli. Here also stasis and necrosis result. Microscopically the tissue in infarcted areas has the usual appearance of necrotic tissue, nuclei being absent and the tissue staining with the acid dye. An exception to the appearance of ordinary necrosis is that usually the structure of the affected organ is at first to be made out perfectly. In lung and spleen infarcts the infiltration of the tissue with red blood corpuscles is of course a prominent feature. As the infarct grows older, signs of reaction on the part of the surrounding tissue, the wandering in of leukocytes, and proliferation of the connective-tissue cells, become apparent.

In a good many instances infarction occurs only during the terminal stages of disease, but sometimes patients survive for a long period after it

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has occurred. In such patients infarctions undergo a process of organization similar to that already described under Thrombosis, and as a result the infarct is replaced by a cone-shaped patch of scar tissue very much smaller than the original infarct. Such scars are common enough in the kidneys, are less common in the spleen, and are rare in the lungs, as pulmonary infarcts are almost always forerunners of death. Certain bland emboli, such as air, fat, and parenchyma cell emboli, produce special effects, and will be considered under separate headings.

The effect of the lodgement of the so-called active emboli depends on their nature. The most important of them are the infective emboli, emboli of tumor cells, and parasitic emboli.

Infective emboli produce the same mechanical effects as bland emboli, and in addition changes due to the action of the contained bacteria and their toxins. As in other infections two factors are to be considered: the virulence of the infective agent, and the local and general resistance of the individual. Inasmuch as the virulence of the bacteria in infective emboli may be slight, and the resistance of the individual to infection may be great, we find that many infected emboli produce only mechanical effects. It is to be noted that not only the general resistance, but also variations in the local resistance of different organs, are to be reckoned with. Such variations differ to some extent in individuals of the same species, and to a more marked extent in individuals of different species. Where the individual resistance is lowered or the bacteria in the emboli possess a high grade of virulence, we see, besides the ordinary mechanical effects, the production of hemorrhages, of extensive necrosis, of metastatic abscesses in the tissues in which the emboli lodge, and, if putrefactive bacteria are present, of areas of gangrene.

Embolic Aneurisms.—One of the rarer complications of embolism is the production of embolic or mycotic aneurisms. Such aneurisms usually occur as a result of the direct action of pyogenic bacteria contained in infected emboli on the walls of the affected artery. This causes a partial destruction of the coats of the vessel and a consequent weakening. Rarely the traumatic action of sharp emboli of calcific material may lead to aneurism formation, but the view now generally held is that this form is very unusual. These aneurisms may develop upon any vessel, but are naturally more prone to occur in those vessels which are lacking in support from surrounding tissue. They are more common for this reason in such arteries as the mesenteric, the more superficial peripheral arteries, and the cerebral arteries. The aneurisms are usually associated as secondary phenomena with general sepsis, especially sepsis with endocarditis, but the endocarditis is not necessarily present, as sepsis may lead to arterial lesions without affecting the endocardium.

Of the other varieties of active emboli, those of tumor cells and of animal parasites deserve brief mention. Tumor cells may gain entrance to the circulation either by direct growth into the bloodvessels or indirectly by way of the lymphatics and the right heart. In some types of tumor, notably certain neoplasms of the testicle and kidney, it is not unusual for extensive growths to penetrate the veins, from which they may extend even to the cavities of the heart. Large masses may be detached from such tumor thrombi and may cause fatal embolism of the pulmonary arteries. Ordinarily, however, tumor emboli are small, so small that they are more apt to lodge in the capillaries than elsewhere. Those originating in the general circulation usually gain entrance to the veins and naturally tend to be arrested in the

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lungs, although probably a fair percentage of them pass the large pulmonary capillaries and get into the general arterial circulation. As Zahn has shown, paradoxical emboli of tumor cells are not very uncommon. In the case of tumors of the abdomen arising in organs whose vessels drain into the portal system the liver is naturally the seat of the most extensive deposits of neoplastic emboli. There is evidence that after lodgement a good many tumor-cell emboli die, but in many instances they proliferate and cause metastases, although the actual microscopic demonstration of the embolic origin of these is not very common. As was the case with bacteria, so with tumor cells, certain organs seem better suited as soil for growth than others. Aside from the lungs and liver, the bones, the kidneys, and the skin seem especially liable to be the seat of such secondary embolic nodules.

As has been mentioned, certain animal parasites or their ova may act as emboli. Of the smaller ones, the malarial parasite is the most common. In the pernicious type of malaria, the capillaries of the brain are often plugged with parasites. Occasionally they accumulate in the kidney vessels, as shown by Ewing, and the writer saw one case in which the smaller pulmonary vessels appeared as if injected with them. The *Amœba dysenteriæ* has also been observed in the bloodvessels, and some amœbic abscesses of the liver probably originate from emboli of amœbæ in the branches of the portal vessels. Emboli of the larger parasites or their ova are more common in the lower animals than in man, although the *Trichina spiralis* during certain stages of development occupies the vessels, as evidenced by the œdema which accompanies trichinosis. In the dog and the calf the ova of certain strongyloid worms produce emboli, which are often followed by the formation of pseudotubercles. In man echinococci occasionally act as emboli, and in the lungs are stated to produce special symptoms.[1]

Symptoms.—The symptoms produced by the lodgement of an embolus vary according to the character of the obstruction and the function and structure of the tissue involved. Certain symptoms of a local and general character common to all varieties of emboli may be briefly mentioned here. Pain is an almost constant accompaniment of embolism of the peripheral vessels, but is less common in embolism of visceral vessels. In many instances it is very abrupt in onset, and the patient may experience the sensation of a sudden painful blow. In some cases it is not very marked, but it may be intense. It is doubtless due at the onset to the mechanical action of the embolus on the nerves of the affected vessel from impact and stretching, but later in infective emboli the direct action of the bacteria or toxins on the vessel wall plays a part. In both bland and infective emboli the anæmia of the area supplied by the embolized vessel also accounts for some of the pain, as it causes irritation of the sensory nerves. Pain of a secondary character, due not so much to the embolism as to the production of inflammation in the involved tissues, occurs in connection with septic emboli. Local evidences of interference with the circulation are not directly visible except in patients with emboli of the vessels supplying the extremities or surface of the body. They may appear indirectly, however, in pulmonary embolism in the form of hæmoptysis, in mesenteric embolism, as hemorrhagic diarrhœa, and in embolism of the renal artery, as hæmaturia. Evidences of impairment of function in visceral embolism are often slight or absent, except

[1] Garnier and Jomier, *La presse méd.*, 1905, i, 369.

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in the case of organs such as the central nervous system, in which definite functions are associated with sharply localized areas. Even here embolism of the vessels supplying the so-called silent areas might produce no evidence of disturbed function. Embolism of the vessels of other internal viscera may be accompanied by impaired function if large areas are thrown out of action. If only a small area is affected the lesion is compensated for by the uninvolved portions of the organ, or in the case of paired organs, by the normal one. General symptoms such as chills, fever, headache, and rapid heart's action, are not usually marked except in connection with septic emboli, and are due to the sepsis rather than to the embolism. Slight fever and acceleration of the pulse may occur as a result of bland emboli. The symptoms produced by special forms of embolism and by special localizations will be discussed more at length in the following pages.

Air Embolism.—The association of sudden death with the entrance of atmospheric air into the veins has long been known to surgeons. As a rule it only occurs when veins of a fair size and situated near the heart are opened. It is therefore especially liable to occur in connection with operations on the neck, not only because the veins of the neck are near the heart, but also on account of the fact that these vessels are held open by their relation to the fascia, and because the aspiration of the thorax acts forcibly here and tends to suck in relatively large quantities of air in a short time. Air embolism has also been described in connection with wounds of other superficial veins, usually of the upper extremities or the head, and as a complication of operations on the uterus during the puerperium, or even of simple intrauterine douching. Rarely air embolism has been reported as a complication of gastric ulcer.

There is little doubt that a large number of supposed cases of air embolism will not stand critical inspection. Welch and Flexner[1] pointed this out in 1896, in an article on the *Bacillus aërogenes capsulatus*. They say: "It is not a little remarkable that of the considerable number of reported cases of suspected entrance of air into the bloodvessels, none seem to have been previously the subject of bacteriological study." In his article in Allbutt's *System*, Welch reiterates the view that many instances described as air embolism are in reality infection with gas-producing bacteria. This view is strongly supported by Schmaus and others. Cases of supposed air embolism after labor or in connection with diseases of the gastro-intestinal tract must be scrutinized with special care, for in both these situations infection with the *Bacillus aërogenes capsulatus*, the commonest cause of gas in the vessels, has been shown to be not infrequent.

Making due allowance for infection with gas-forming bacteria, there remains a certain number of cases in which no doubt exists that the entrance of air into the veins caused death. Experimental work on the lower animals has shown that it is possible to cause death in this way, although in dogs, the animals usually employed, large amounts of air are required, and the chances of producing a fatal result are greater the nearer the heart the air is introduced. The cause of death according to Wolf[2] is nearly always pulmonary embolism, although occasionally coronary or cerebral emboli cause the fatal result. As a rule the air does not penetrate beyond the pulmonary

[1] *Journal of Experimental Medicine*, 1896, No. 1.
[2] *Virchow's Archiv*, 1903, vol. clxxiv.

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capillaries, and Wolf seems inclined to throw out of the category of air embolism cases in which air was found in any quantity in the general circulation.

The *symptoms* of air embolism in well-marked cases are striking and easily recognizable. Usually during the course of an operation on the neck the surgeon is suddenly startled by the sound produced by the entrance of air into a severed vein. This is described by Koenig as a "lapping" murmur. In some instances the patient dies with lightning-like rapidity; in others death is preceded by signs of apprehension, dyspnœa, cyanosis, trembling, dilatation of the pupils, syncope, and convulsions. A distinct churning sound, which Wolf believes is due to the mixture of air and blood being pressed behind the columnæ carneæ or being forced through the pulmonary valves, may be heard in many cases on auscultating over the heart. The symptoms last but a few seconds, and most patients die, although recoveries are recorded. The cases of Janeway and Hun, in which cerebral symptoms followed the introduction of peroxide of hydrogen into the thoracic and abdominal cavities respectively, should possibly be classed with air embolism.

Fat Embolism.[1]—Most commonly met with after fractures of the long bones, emboli of fat have also been encountered after orthopedic operations, especially brisement forcé, after ordinary surgical operations and operations on the bones, after contusion or laceration of the subcutaneous fatty tissue, and in association with infections with fatty degeneration of the organs, with atheroma of the arteries, and with diabetes mellitus. The complication has also followed the subcutaneous introduction of oil for purposes of nutrition. The view generally held regarding the origin of fat emboli associated with fractures has been that they originate as a direct result of the entrance of fat into the vessels at the point of local injury to the bone. Ribbert[2] claims that the amount of fat found in the lungs is too great to have originated in this way, and he explains the lesion as due to the escape of fat from the general jarring of the bones. The fat emboli are found in some patients merely in the lungs; in others, after an interval of one or more days, some of the emboli pass on and lodge, according to Ribbert, especially in the muscle of the right side of the heart and in the brain. In these situations they produce areas of hemorrhage and fatty degeneration sufficient perhaps to account for the cardiac and cerebral symptoms. The emboli also lodge in the spleen and kidneys, although here they do not produce any appreciable symptoms except that fat is commonly excreted with the urine in the case of kidney involvement.

Symptoms of fat embolism are in many instances lacking, although in severe cases sudden death may ensue. In a certain number of patients symptoms definite enough to allow of a diagnosis occur. These do not appear immediately after the injury, but are delayed from six hours to fifteen days. Usually the patient, who has perhaps reacted from the shock of the fracture or operation, is noticed to be breathing more rapidly than normal, appears anxious, may be restless, or on the other hand somnolent, and may complain of pain in the side. Sometimes hæmoptysis is present. Physical examination will show in such patients the appearances often ascribed to shock; pallor, perhaps cyanosis, a cold skin and a rather feeble, rapid, and irregular pulse, and probably slight elevation of the temperature. In severe cases contracted

[1] Connell, *Journal of the American Medical Association*, February 25, 1905.
[2] *Deutsch. med. Woch.*, June 28, 1900.

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pupils, diminished reflexes, Cheyne-Stokes respiration, convulsions, and coma may occur, and death may close the scene. Localized signs of consolidation of the lung with a few rales may be present. They are most apt to be heard posteriorly over the bases of the lungs, The presence of fat in the urine is an important diagnostic sign, and fat may be found in the sputum also. In a patient recently seen with my colleague, Dr. Sanford, there was a slight leukocytosis, 14 per cent. of the cells being neutrophilic myelocytes.

The *prognosis* is, as Connell remarks, uncertain, as we do not know the frequency of fat emboli. The mortality from this cause after fractures is probably not over 1½ per cent. The diagnosis of the condition is not necessarily difficult. It may be confused with shock or with ordinary embolism, but shock occurs much sooner after the operation or injury than does fat embolism, and ordinary emboli are a late complication. The presence of fat in the urine is of diagnostic value, but may occur after fractures without symptoms of fat embolism. If associated with localized lung signs, slight fever, rapid pulse, and respiration, and mental unrest or somnolence, these symptoms appearing from six to seventy-two hours after a fracture, the probabilities are in favor of fat embolism. In operative cases the differentiation from the effects of anæsthetics may be difficult, and sepsis might be suspected in patients with a good deal of fever.

Cell Emboli.—Apart from emboli of tumor cells, there have been described for the last twenty years or more emboli composed of the cells of normal organs or tissues, and more recently emboli of phagocytic cells associated with infectious diseases. Of the normal cells, those of the liver, placenta, and the bone-marrow are the most commonly found as emboli.

After injuries, not only cells but actual fragments of liver tissue and bone-marrow may be transported, and even whole chorionic villi have gained access to the circulation. In typhoid fever large phagocytic cells may gain entrance to the portal circulation, as the studies of Mallory[1] show, and MacCallum[2] has demonstrated that the same cells may enter the lungs through the thoracic duct. Most cell emboli lodge in the pulmonary vessels, but a few reach the general circulation through an open foramen ovale. These emboli are not usually large enough to cause lesions of an extent sufficient to produce clinical symptoms. They do in some instances lead to secondary thrombosis as would be expected, for some of the cells contain thrombokinase. Those which lodge in the liver in typhoid fever probably play an important role in the production of the focal necroses which occur in this disease. Occasionally, as in the patient reported on by MacCallum, cell emboli may cause quite extensive pulmonary infarction.

Mercurial Emboli.—The introduction of the use of insoluble mercurial salts by the hypodermic route was soon followed by evidence that embolism at times resulted. The accident occurs after the use of the salicylate of mercury, of gray oil, of calomel, and of other insoluble preparations, especially when paraffin is used as a vehicle. The frequency of the complication is hard to judge, as fatal cases are extremely rare. Voss[3] could only find one fatal instance of mercury embolism recorded. Most of the statistics as to frequency are compiled from evidence of lung complications following the

[1] *Journal of Experimental Medicine*, 1898, vol. iii, No. 6.
[2] *American Medicine*, March 21, 1903.
[3] *Dermatolog. Zeitschrift*, 1904, p. 473.

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injections. Möller claims that evidence of embolism occurs in one patient of every 11 treated. Voss states that these figures are too high, and gives 1 embolism for each 91 patients, as a result of his studies. A collection of the records of 2281 patients treated by injections of mercury showed that the complication was present in a little under 1 per cent.

The symptoms of mercurial embolism depend upon the point of lodgement in the lungs, the emboli which lodge peripherally causing involvement of the pleura and therefore pain. In such cases the characteristic symptoms are the sudden onset, soon after the injection, of paroxysmal cough, with lancinating pain in the side, sometimes chilly sensations, and usually fever. In some instances no symptoms appear for at least twenty-four hours after the injection. Fever may be absent, and, if the emboli are deep-seated, pain is not usually present. The physical signs of a patch of consolidation associated with rales may sometimes be detected. The diagnosis is obviously simple, although it must be borne in mind that in cases of fresh luetic infection fever, chilly sensations, and anorexia may follow the injection of mercury without the presence of lung emboli. The prognosis is so uniformly good that some syphilographers take it for granted that the complication will occur and consider it no obstacle to the hypodermic use of mercury. According to Heidensfeld, of Cincinnati, embolism may be avoided by using lanolin as a vehicle for the mercury.

Paraffin Emboli.—It may be briefly pointed out here that the subcutaneous use of paraffin for cosmetic purposes, especially for the repair of nasal defects, has been followed in several instances by paraffin embolism of the central artery of the retina. The cases recorded in the literature are not numerous, but this complication is more frequent than the reports would indicate, and on account of its gravity must be recorded. The complication usually ensues immediately after the injection of the paraffin. The patient may show marked symptoms of collapse and sudden loss of sight on one side. The loss of vision is usually permanent. According to Stein[1] the complication may be avoided by using only soft paraffin, injecting it only when it has a pasty consistency, and never using more than 3 cc. at a sitting.

Embolism of Special Arteries.—Embolism of the Pulmonary Artery.—Embolism of the pulmonary artery is, according to most authorities, the most frequent form of embolism and is much more common than thrombosis of this vessel. Certain observers, Ribbert and Newton Pitt, for example, incline to the view that thrombosis of the pulmonary artery is much more common than is usually taught. Lubarsch's figures seem to disprove this. He found in 800 autopsies, obstruction in the pulmonary arteries in 116, and of these 105 were evidently of an embolic nature, leaving only 11 of thrombosis. Pulmonary emboli occur most frequently in connection with heart disease, in this instance usually originating from emboli in the right side of the heart, and in connection with certain forms of peripheral venous thrombosis, especially the puerperal type and some other varieties already mentioned in the article on thrombosis. Occasionally pulmonary embolism arises from the detachment of portions of parietal thrombi in the larger branches of the vessel itself. The symptoms produced by the lodgement of an embolus in a branch of the pulmonary artery depend mainly upon the size of the vessel which is obstructed. Blocking of the trunk or of one of

[1] *Deutsch. med. Woch.*, 1903, vol. xxxix, Nrs. 36–37.

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the main branches usually results in sudden death. This may occur with lightning-like rapidity, but is often delayed a few seconds, during which time the patient is almost apnœic, is gasping for breath, deadly pale, and practically pulseless. The sufferer may cry out at the time of lodgement of the embolus, and may grasp the precordial region with an expression of great anguish. In a few rare instances, as those reported by Hart,[1] occlusion of the main trunk has occurred without causing immediate death and without causing marked changes in the lungs.

Where a medium-sized branch is plugged, or where an embolus lodges in a large branch, but does not completely occlude the lumen of the vessel, the patient may survive for hours or days, or may even recover completely. The most prominent symptoms in these patients are the rapid respiration and the marked dyspnœa, both of which in the early stages are out of all proportion to the signs of pulmonary involvement. The dyspnœa and the intense sensation of oppression in the chest which accompanies it, recall ordinary cardiac asthma, but the rapidity of onset of the symptoms in embolism and their great intensity are points of distinction. Lancinating pain in the chest may be present in patients with embolism of this type, but it is unusual. It may be absent at first, but present later in patients who survive long enough for the development of pleural involvement. The physical signs vary in such patients at different periods. At first the patient is pale, later often markedly cyanotic, extremely restless and anxious looking. A marked effect on the circulation is apparent from the first. The heart is weak, perhaps irregular, and the pulse is small, feeble, and very compressible. Systolic and diastolic murmurs at the base of the heart have occasionally been described. Physical signs in the lungs are at first absent. After twenty-four hours, if the patient survives that long, there may be impaired resonance over a part or the whole of one lobe, usually a lower lobe. This is generally accompanied by feeble breath sounds and a few fine moist rales which later may become much more numerous. At the time the definite lung signs develop the patient may have a profuse, frothy, or bloody expectoration, but this usually disappears in a few days. There is often some fever, although this is not as a rule high. The mind is usually clear, although convulsions and coma may precede death in fatal cases. Recovery may occur in patients with severe symptoms. Leopold reports the case of a patient who recovered after three distinct severe attacks.

Obstruction of the smaller branches of the pulmonary artery leads in many instances to the formation of a hemorrhagic infarct. Such infarcts occur in nearly 50 per cent. of all cases on the right side at the base of the lung, and physical signs are therefore to be looked for in the area bounded by the angle of the right scapula, the spinal column, and the diaphragm. In 33 cases analyzed by Tiedemann[2] the right lower lobe was involved in 15, the right upper lobe in 7, the left lower lobe in 5, the left upper lobe in 4, and the right middle lobe in 2. This form of pulmonary embolism is almost always associated with cardiac rather than peripheral thrombosis, and usually occurs in patients with cardiac disease and failure of compensation.

Symptoms of pulmonary infarction are not always present. In some instances the lesion is entirely latent. In other cases the symptoms which

[1] *Deutsch. Arch. f. klin. Med.*, 1905, vol. lxxxiv.
[2] *Zeit. f. klin. Med.*, 1903, vol. l.

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accompany the embolism of a large pulmonary vessel are present in a modified form. There is a sudden attack of pain in the side, usually the right, with a rigor or chilly sensations, an increase in dyspnœa, a rise in the temperature, and perhaps bloody or, at any rate, blood-streaked expectoration. True hæmoptysis in the sense of the expectoration of pure blood is rare, but blood-streaked sputum is not uncommon, and should always suggest infarction in a patient with heart disease in the stage of broken compensation. Physical signs can be detected in a great many patients with pulmonary infarction, as the lesion is most common at the bases of the lungs, which are accessible to exploration, and because most infarcts involve the periphery of the organ so that there is no zone of normal lung tissue between the lesion and the ear of the observer. The detection of certain signs, such as definite dulness or changes in the fremitus, depend on the size and situation of the infarct. Obviously no definite signs are to be made out by inspection. On palpation, as a rule, marked signs are absent, although under unusually favorable conditions, *i. e.*, a large infarct superficially situated, the fremitus is said to be generally decreased. On percussion one or more circumscribed areas of dulness may often be made out. The dull note not infrequently has a tympanitic quality, this being due at times to the collapsed condition of the lung about the infarct and at times to the transmission of resonance from a large bronchus through the consolidated lung. Tiedemann states that the tympany is not due to œdema about the infarcted area, as has been claimed by Gerhardt and others. Auscultation over the infarcted area during the early stages may reveal fine crepitant rales, although these do not usually last long, since the area soon becomes completely consolidated. The breath sounds over the area of consolidation may be feeble or almost lacking, or, if the area is in contact with a fair-sized bronchus, there may be marked bronchial breathing. As a result of atelectasis of areas about the infarct, crackling rales may be heard in its neighborhood. A pleural rub may be heard when the infarct is superficial. The detection of an area consolidation may be interfered with by signs due to the widespread bronchitis often found in chronic heart disease, or by the presence of a pleural effusion.

The *diagnosis* of pulmonary embolism involving the larger vessels is based on the sudden onset of intense pulmonary symptoms in a patient suffering from some disease which is commonly associated with venous or cardiac thrombosis. The more prominent of these diseases and the frequency of their association with embolism has been noted in the article on Thrombosis. In women the puerperal state and chlorosis should always be regarded with suspicion, and in both sexes patients should be watched during and after the infectious and cachectic diseases, local diseases of the veins, cardiac disease, and abdominal operations. The actual source of the emboli in many cases of pulmonary embolism is obscure.

The *prognosis* in pulmonary embolism is always grave. In the puerperal form 60 per cent. of the patients die, according to Richter. Embolism in chlorosis has a prognosis even graver than this. Recovery from embolism of the larger branches of the pulmonary artery is very rare, although it does occur. Recovery after smaller emboli with infarction is also uncommon. According to Romberg, of 43 patients with heart disease and signs of lung infarction observed in his clinic, 36 died. The prognosis depends not only upon the size and character of the embolus, but also upon the general condition of the patient.

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Embolism of the Splenic Artery; Splenic Infarction.—The appearance of an infarct in the spleen is often unaccompanied by clinical symptoms or signs sufficient to allow of its detection. In some instances the diagnosis can be made. The most important diagnostic signs are the occurrence of sudden pain in the splenic region, with enlargement of the spleen. Sometimes the onset of symptoms is accompanied by a definite rigor. Vomiting is not uncommon, according to Leube. The pain is not always present. The swelling of the spleen is not usually very marked, but the organ is generally palpable, and there may be a localized point of special tenderness with an overlying friction rub due to localized peritonitis. Fever is not marked unless the infarct is a septic one, in which case there may be a high fever a few days after the onset of signs, and chills may occur. When suppuration follows a septic embolus, marked signs of local peritonitis may occur and there may be general peritonitis from rupture of the purulent focus. Even with bland emboli there are sometimes very marked signs of local peritonitis, as in the case reported by Riebold.[1] The presence of a source for embolism or of signs of emboli elsewhere will, of course, have great weight, and will make the diagnosis of splenic infarct more certain.

Renal Infarction.—Like splenic infarction, renal infarction may be latent. In some instances, however, definite evidences of kidney involvement are present. The most important of these are changes in the urine and pain and tenderness in the kidney region. In bilateral infarction of the kidney there may be complete suppression of urine, but this never occurs, according to Schmidt,[2] in unilateral infarction. As a rule there is some diminution in the quantity of urine, with the presence of large amounts of albumin and perhaps some blood. Schmidt states that hæmaturia is quite uncommon. It is perhaps overlooked in some instances. In a patient recently seen with Dr. Lindsley, an old lady with myocarditis and broken compensation, there was hæmaturia with albuminuria coming on suddenly with pain in the back, and lasting only two days. This was almost certainly due to embolism, as the urine had been previously clear. The case illustrates how easy it is to overlook urinary changes unless frequent examinations are made. The absence of casts or marked sediment may be a striking feature of albuminuria from embolism, and is probably due to the fact that no urine is secreted in the infarcted area and nothing is therefore washed out of it. The occurrence of pain is not infrequent in connection with kidney infarcts. The pain is sometimes intense, requiring the liberal use of morphine. At other times it is described as burning or as a sensation of pressure. Its very sudden onset is often suggestive. It is situated as a rule in the kidney region, radiates but little, and is never referred to the external genitals or to the shoulder-blades. It is more constant than the pain of ureteral calculi. The pain is associated with marked tenderness in the kidney region on the affected side, and may be increased by coughing, deep breathing, and vomiting.

The *symptoms* of kidney infarct may be confounded with those of Dietl's crisis from movable kidney, with pain accompanying the sudden congestion of a tumor of the kidney, or with the pain of an acute exacerbation of a chronic nephritis. The pain in the infarct is usually more severe than that

[1] *Deutsch. Arch. f. klin. Med.*, 1905, vol. lxxxiv.
[2] *Wiener klin. Woch.*, 1901, vol. xiv.

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accompanying an exacerbation of an old nephritis, and is more marked on pressure. The high-tension pulse and cardiovascular signs of nephritis are absent in renal infarct, and the presence of large amounts of blood in the urine is also unusual in this condition. The onset of a Dietl's crisis often follows exercise, while the pain of infarct often appears while the patient is in bed. Other conditions, such as gallstone colic, lead colic, and ureteral colic might cause confusion, but the differential points readily suggest themselves. Evidence of some source for an embolus is in any case very important before making a diagnosis of renal infarction.

Embolism of the Mesenteric Arteries has been considered under the head of Thrombosis.

Embolism and Thrombosis of the Aorta.—Embolism and thrombosis of the thoracic aorta are of extremely rare occurrence, for with the great force of the blood stream through this part of the circulation it is only very exceptionally that a thrombus can form or an embolus gain lodgement. Complete obstruction of the thoracic aorta is followed by death, usually very suddenly, at latest after a few hours. Incomplete obstruction either produces no appreciable symptoms, or, if marked, leads to the same changes which characterize obstruction of the abdominal aorta together with, in some instances, signs of blocking of the arteries of the upper extremity.

Embolism and thrombosis of the abdominal aorta are best considered together, for although there exist instances in which the gradual progress of the disease seemed to show that thrombosis was the lesion, it is often impossible either from the clinical history or from the pathological findings to determine whether the obstruction is due to a thrombus or an embolus. There is evidence, in fact, that thrombosis of the aorta may suddenly give rise to very acute symptoms and that embolism may rarely occur without signs of sudden onset. The small parietal thrombi of the aorta which are not uncommon in connection with patches of sclerosis are not referred to here. This discussion relates to the large occluding plugs occupying as a rule that portion of the abdominal aorta which lies below the point of origin of the main branches, *i. e.*, below the origin of the mesenteric arteries. This part of the vessel is considerably narrower than the rest of the main trunk and is the section in which, under conditions of enfeebled circulation, the best chances for the formation of a thrombus or the lodgement of an embolus are to be found. Most cases of aortic thrombosis are associated with disease of the vessel wall, usually arteriosclerosis, while of the cases which appear to be embolic—and these constitute a large majority—the greatest number are associated with mitral stenosis. When this latter lesion is present there is frequently evidence that thrombosis has been present somewhere in the left side of the heart, and whilst this is sometimes lacking, aortic emboli originate in most instances in this situation. In other cases external pressure plays a part, or the embolus is furnished by a thrombosed aneurism of the thoracic aorta.

The *symptoms* of obstruction of the aorta vary. The affection is stated to be occasionally latent, but this is not to be interpreted to mean that it is entirely devoid of symptoms. It would be more correct to say that in some patients symptoms are obscure and cannot be definitely referred to a lesion of the aorta. In patients with definite symptoms, these may be gradual or sudden in onset. When the onset is gradual it is believed by some observers, the French school especially, that the patient may survive two, three, or even four years after the appearance of the first symptoms. Certain writers

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lay stress on the importance of intermittent claudication as an early sign of the gradually progressing form of thrombosis of the abdominal aorta.[1] As the disease progresses this symptom becomes more and more marked and may be associated with severe pain in the lumbar region radiating to the limbs. There may be sensations of numbness and formication in the feet. Finally a paraplegia of the lower extremities develops, usually followed by gangrene of parts of one or both lower limbs. The character of the paraplegia is not well described in many of the reports. Usually it seems to be incomplete, limited movements of the limbs being possible. The state of the reflexes varies; in some patients they are abolished; in others, the paralysis being spastic, they are presumably increased. The occurrence of gangrene is preceded first by coldness and pallor, later by cyanosis of the extremities, and in some cases by chronic ulcerations. Usually severe pain in the legs is an accompaniment of the gangrene. The extent of the mortification varies in different patients, this probably depending in part on the completeness of the obstruction of the aorta, in part on the number and distribution of collateral vessels. Œdema is not as a rule marked in these patients, and may be absent.

In patients in whom the onset of aortic obstruction is acute—and these constitute the majority—pain is usually the most prominent of the early symptoms. The pain is generally intense and referred to the lower extremities. The patient may be struck as by a shock and fall to the ground in intense anguish. In most instances there is a markedly anxious expression of the face as a result of this. Occasionally pain is absent, and, on the other hand, it sometimes occurs in paroxysms separated from one another by periods of several days. Aside from the pain, other symptoms in the acute cases are very variable. Usually there is pallor of the skin of the extremities, followed by lividity, diminution of sensation, paresis and finally paralysis of the muscles, and gangrene. The pulsation in the vessels of the legs is naturally very feeble or entirely absent. General symptoms may occur. The intense pain may cause marked psychic disturbances. There is sometimes a gradual rise in the temperature. The pulse usually becomes distinctly weaker and more rapid than it was before the onset of the symptoms of aortic obstruction. If the renal vessels are involved symptoms of renal infarction or even total suppression of urine may occur. Involvement of the mesenteric arteries will produce the intestinal symptoms already described under Mesenteric Thrombosis. Pain in the lower abdomen and tenderness over the aorta are not infrequently present.

In the *diagnosis* of a typical case there would hardly be any doubt. The distinction between an embolus and a thrombus, as already stated, cannot be made. Some of the more chronic cases might, at some stages, suggest Raynaud's disease, but the fact that only the lower extremities are affected, the progressive character of the lesion, and the lack of arterial pulsation should rule this out. In patients without much pain an acute myelitis might be suggested, but the pallor of the skin, the cold lower extremities, and the absence of pulsation in the vessels of the legs should prevent this mistake.

The *prognosis* is exceedingly grave. Very few patients have recovered, Death may take place the same day that the symptoms appear; usually the end comes within fifteen days from the onset. Some patients, however,

[1] Mazoux, *Thrombosé de l'Aorte, Thèse de Paris*, 1905.

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live several weeks, and a few survive several years after the symptoms first manifest themselves.

Embolism and Thrombosis of the Subclavian Artery.—Embolism of the large branches of the arch of the aorta is extremely rare, most instances of obstruction being due to thrombosis associated with narrowing of the origin of the vessel from arteriosclerosis.

The *symptoms* of obstruction of the subclavian artery are very variable, and, considering the size and importance of the vessel, the lack of striking symptoms is often the most marked feature. The subjective symptoms may be very slight. There may be neuralgic pain of a paroxysmal character in the neck and shoulder on the affected side, and this may be markedly influenced in some patients by changes in the weather. Occasionally there is distinct weakness of the arm. This may almost amount to a paralysis in some instances. The objective signs are the result of the obstruction to the circulation. The pulsation in the radial artery on the thrombosed side is in some instances not influenced in the least; in other patients the *pulsus differens*, such as is found in some cases of aneurism and occasionally in dilatation of the left auricle, may occur. The pulsation in the carotid artery on the affected side is usually unimpaired, although it may be a little weaker than normal. In some patients changes in the skin are present in the form of great dryness, or sometimes a patchy œdema. There may be a wasting of the muscles of the arm on the affected side. Gangrene is usually absent, and its presence is stated by Hoegerstedt and Nemser to usually indicate that the process is a luetic one. The *diagnosis* can only be positively made during life by palpation of the arteries on each side with the demonstration of lack of pulsation in one of them. In a few instances the thrombus may extend into the axillary or brachial arteries and these vessels may then be felt as firm cords.

Embolism and Thrombosis of the Carotid Artery.—Embolism of the common carotid artery is very unusual, the internal carotid being much more frequently affected. Thrombosis is more common than embolism, and, like thrombosis of the subclavian artery, it is usually associated with arteriosclerotic changes in the vessel wall. Occlusion of the carotid is of interest clinically mainly on account of its relation to the cerebral blood supply. As has been abundantly proven by ligature of the vessel during operations on the neck, the effect of obstruction on the cerebral circulation is usually slight, not infrequently entirely negative. The anastomoses with neighboring vessels are extensive, the most important in the case of the external carotid being the branches from the carotid of the other side; in the case of the internal carotid, the vertebral arteries and the circle of Willis. In some instances the collaterals seem to be poorly developed or unable to accommodate themselves to the increased demands, and symptoms of cerebral anæmia and softening occur. The patient may complain of giddiness, and there may be convulsions, stupor, coma, and eventually hemiplegia on the side opposite the lesion. In some patients there is paralysis of one side of the face only or of one limb. Aphasia may follow thrombosis of the left carotid artery. The diagnosis may sometimes be made during life by detecting the thrombosed vessel as a sensitive cord. Here, as in other forms of vascular obstruction, the rapidity with which occlusion of the vessel occurs has a bearing on the development of symptoms, and embolism is, for this reason, more apt to produce serious symptoms than thrombosis.

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Embolism and Thrombosis of the Arteries of the Extremities.—A distinction between embolism and thrombosis of the arteries of the extremities is sometimes possible from the fact that in some patients with arterial thrombosis the onset of the symptoms is gradual. Of recent years, however, less and less weight has been placed upon the manner of onset as a criterion of the character of the lesion, especially as it has been shown that the onset of symptoms in thrombosis is frequently just as abrupt as in embolism.

The *symptoms* of obstruction of the peripheral arteries are similar in many ways to those of venous obstruction in the same situation. They depend largely on the number of anastomosing vessels and the rapidity with which a collateral circulation is established. In general it may be stated that the result of plugging of peripheral arteries is less marked in the upper extremities where the collaterals are numerous, but the result depends not only upon this, but also on the condition of the circulation in general and upon the presence or absence of vascular disease. Naturally the obstruction of an artery, other things being equal, will produce quite different effects in a young, relatively vigorous individual with sound arteries and in an old, feeble person with diseased vessels. Pain is a symptom which is practically always present, is usually sudden in onset, and is often extremely severe. It is directly due to the stretching of the vessel, and in cases of embolism also to the impact of the embolus. As a rule it is associated with disturbances of sensation in the part rendered anæmic in the form of hypæsthesia or complete anæsthesia, and disturbances of motion ranging from paresis to complete paralysis due to insufficient supply of blood to the affected muscles. The affected limb is usually at first pale and cold, and although œdema is often present, it is generally slight and not to be compared in extent to the œdema of venous thrombosis. Palpation of the affected artery below the point of embolism demonstrates a lack of pulsation, an extremely important sign of arterial obstruction. Tenderness of the vessel is also usually present. As time goes on, if the collateral circulation is not established, the pallor of the limb changes to cyanosis or a mottled appearance, and finally gangrene occurs. If the embolus is infective we see, besides these changes due to mechanical obstruction, perivascular suppuration, and perhaps the formation of an embolic aneurism.

The differentiation of arterial thrombosis from arterial embolism is, as stated, often impossible, nor is it of any particular importance. The differentiation of embolism from venous thrombosis is usually easy. Pain is common to both, but in embolism lack of marked œdema, the loss of arterial pulsation, the more marked sensory symptoms and paralysis, and above all the gangrene, usually leave little room for error. Besides this, a source for the embolus can frequently but not invariably be made out.

So far as the loss of a limb is concerned, the *prognosis* depends upon the artery affected and the general condition of the patient. Plugging of the arteries of the upper extremity is less serious than obstruction of the vessels of the legs. Thrombosis or embolism of the femoral or popliteal arteries almost invariably results in gangrene, whereas even the subclavian may be obstructed without gangrene of the hand or arm. Gangrene is much more apt to occur in patients with an enfeebled circulation and preëxisting arterial disease. If a patient is already enfeebled and shows evidences of embolism elsewhere, the obstruction of a peripheral artery may be the direct cause of a fatal termination. Naturally the arterial obstruction resulting from chronic

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heart disease with failing compensation is much more serious than that following the infectious diseases.

Obstruction of the Hepatic Vessels; Hepatic Infarction.—The types of thrombosis of the hepatic vessels associated with clinical symptoms have already been discussed. Brief mention must be made here of the infarcts of the liver which, however, are not known to be associated with distinct clinical features and are of pathological significance only. Two forms of liver infarction are to be recognized: the white infarct, usually due to obstruction of a branch of the hepatic vein, but occasionally resulting from portal obstruction or rupture of the liver, and the so-called "atrophic red infarct" of Zahn, which occurs in certain cases of thrombosis or embolism of the branches of the portal vein.

The white or anæmic infarcts are much less frequent than the red ones. In cases of obstruction of the main trunk of the hepatic artery the whole liver may be infarcted and undergo total necrosis. Usually only small branches are affected and the infarcted areas appear as small, nodular, necrotic masses scattered through the organ, or as definite cone-shaped areas in the periphery. Under the microscope such areas show complete necrosis of the liver cells, with retention of the architecture of the organ, the wandering in of leukocytes, and ultimately, in some instances, evidences of organization.

The atrophic red infarcts are much more common than the anæmic ones, and in many instances have not the microscopic structure of true infarcts at all. They occur, according to Steinhaus,[1] when there is obstruction to the branches of the portal vein associated with feebleness of the general circulation, with resulting impairment of the blood flow in the hepatic arteries. The red infarcts may be peripherally situated, elevated, and wedge-shaped, but are quite often depressed below the surface of the liver. They present the appearance under the microscope of localized areas of chronic passive congestion, with marked dilatation of the vessels and atrophy of the liver cells. According to Chiari they may sometimes undergo a process of organization beginning as encapsulation and terminating in the replacement of the infarcted area by a patch of scar tissue.

Embolism and Thrombosis of the Coronary Arteries of the Heart.—Most authors are agreed that thrombosis of the coronary vessels is much more common than embolism. In view of the situation of the origins of the coronary arteries, their size, and the frequency with which degenerative changes attack their walls, it would seem that the chances in favor of thrombosis are much greater than those in favor of embolism. A few observers, Romberg for example, state that the large and medium-sized coronary vessels are most frequently obstructed by emboli, but the mass of pathological evidence contradicts this. When thrombosis does occur, it is associated in a great majority of instances with arteriosclerosis of the coronary vessels, and considering the frequency with which this occurs, it is strange that thrombosis is not more common. Embolism of the coronaries is usually associated with general sepsis and endocarditis, and the emboli are therefore usually infective. Bland emboli in the coronaries have been described in a few instances.

Whether the stoppage of the coronary artery is due to a thrombus or an embolus, the result, both from a pathological and a clinical point of view, is much the same, and depends partly on the size and distribution of the

[1] *Deutsch. Arch. f. klin. Med.*, 1904, vol. lxxx.

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occluded branch, partly perhaps on the presence or absence of preceding disease of the vessel and partly on individual peculiarities in the circulation.

Stoppage of the main branch of the coronary artery results in most instances in sudden death. There are, indeed, a few observations on record which show that this is not invariably the result. There may, in fact, be obstruction of the two main branches, as in Thorel's patient, without any marked cardiac symptoms during life. Such instances are no doubt due to individual peculiarities in the circulation, and do not alter the fact that in most patients a fatal issue may be expected from a few seconds to a few hours after the obstruction has occurred. There is some difference in the results, judging from experimental work, according to the vessel blocked. Porter's work shows that obstruction of the circumflex branch is the most dangerous; that the right coronary and the branch to the septum can be obstructed with the least risk, and that obstruction of the descending branch leads to inconstant results. How closely the results of such observations on animals may be transferred to man is questionable, but, as stated above, there is abundant evidence that in the human being obstruction of the main branches of the vessel is, as a rule, quickly fatal.

When obstruction of the coronary artery is not immediately fatal it leads to certain changes in the heart muscle. There may be merely fatty degeneration of the area of muscle supplied by the occluded vessel, but usually an infarction results. The occasional exceptions only go to prove the rule that coronary vessels are terminal vessels, at any rate after they have penetrated the musculature. The common site of the larger infarcts is the anterior surface of the apical one-third of the left ventricle and the septum near the apex, and this because the descending branch of the coronary artery is the one most frequently involved. Occasionally infarcts occupy the wall of the ventricle near its base, and still more rarely the right ventricle is involved. Cardiac infarcts are often irregular in shape, and generally have a characteristic yellowish color and a peculiar dry consistency. They are often hemorrhagic about the edges. On their ventricular surface they are usually covered by a mural thrombus, whilst their pericardial surface is generally the site of a pericardial exudate which may later organize, obliterating the pericardial cavity over the affected area and doubtless affording some protection against rupture and aneurism formation. If the obstruction and resulting infarction are not soon followed by the death of the patient, there may be either a fatal rupture of the heart through the weakened necrotic area, or an organization of the infarct with its replacement by a patch of scar tissue. This may be able to withstand the intracardiac pressure during the remainder of the patient's life, or it may gradually give way with the resulting formation of a cardiac aneurism.

The *symptoms* of obstruction of the coronary vessels are not very characteristic, and it is only rarely that the lesion can be diagnosed during life. The sudden death which often accompanies obstruction of the larger branches is not pathognomonic of thrombosis or embolism, and may, in fact, occur in connection with coronary arteriosclerosis without actual obstruction. On the other hand, the lodgement of an embolus with the formation of a distinct infarction may be clinically latent, especially in individuals with great feebleness of the circulation. There are clinical differences in the way in which death occurs in patients with coronary obstruction. In some the end

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is so sudden and unexpected that, as Krehl puts it, there is not even a change in the facial expression. In other patients the lodgement of a coronary embolus or the formation of a coronary thrombus is accompanied by symptoms of angina pectoris or of severe cardiac asthma. There may be the sudden onset of a severe attack of præcordial pain, with sensations of oppression, great dyspnœa, and a feeling of anxiety. Usually in these patients there is rapidity and weakness of the heart's action, with marked irregularity. In many instances such an attack is followed by death within twenty-four to forty-eight hours, sometimes with symptoms of rupture of the heart. In case the patient survives, the most prominent feature is likely to be a prolonged and gradually increasing cardiac weakness.

The *diagnosis* of coronary artery thrombosis or embolism is at best a question of probabilities. The condition should be suspected when, in an individual who has shown signs of cardiac weakness without marked dyspnœa or pain, a sudden anginal or asthmatic attack occurs followed by death or by a gradually increasing cardiac asthenia. The diagnosis being so uncertain, it is impracticable to discuss the prognosis.

Embolism and Thrombosis of the Retinal Vessels.—Embolism of the central artery of the retina is no longer believed to be so common as was once taught. Many ophthalmologists now hold the opinion that the changes commonly ascribed to embolism are often due to arteriosclerosis or to spasm. The lesion is nearly always unilateral, affects the left eye most frequently, is more common in men than in women, and occurs most often in connection with cardiac disease, although in not a few instances no evidences of a definite heart lesion is present. It is doubtful if the vascular change in most of the last class of patients is thrombosis, though there is incontestable evidence that thrombosis of the central artery may occur. The changes occurring in the retina are essentially those which result in an anæmic infarct elsewhere in the body.

The changes produced by the plugging of the central artery of the retina lead to a characteristic ophthalmoscopic picture. There is a marked ischæmia of the retina, with œdema. The pulsation of the arteries is absent, and these vessels appear collapsed and thread-like. The veins as well as the arteries are at first narrowed, but later may be irregularly dilated. There is commonly a blood-red spot in the fovea, possibly, as Greenwood suggests, due to the contrast between the very thin and non-œdematous retina of this region with the color of the choroid showing through, and the white, œdematous surrounding retina. Another explanation offered by Verhoeff is that the red area is due to hemorrhage. The disturbance in the blood supply to the optic nerve ultimately leads to atrophy.

The most characteristic *symptom* of obstruction of the central artery of the retina is sudden loss of sight. If the obstruction is complete, the blindness is also complete. In partial obstruction there may be tempora ry los of vision followed later by complete loss. If a branch of the vessel is occluded, the loss of sight affects only that portion of the retina supplied by the branch. Inasmuch as the embolism ultimately results in optic-nerve atrophy, the loss of sight is usually permanent. In some patients, either through the establishment of a collateral circulation or as a result of a breaking up and dislodgement of the embolus, a partial return of vision occurs. Thrombosis of the central vein of the retina produces very similar symptoms, although the loss of sight is at first not so marked. In this case the ophthalmoscope shows

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great dilatation of the veins, contraction of the arteries, papillitis with marked hemorrhages, and ultimately optic atrophy.

Diagnosis and Prognosis.—The diagnosis and prognosis of embolism differs according to the location and character of the obstruction, and is discussed under the various forms of embolism, and under Embolism of Special Vessels.

Treatment.—Inasmuch as by far the commonest sources of embolism are venous thrombosis and cardiac disease, preventive measures are to a limited degree possible in many instances. So far as venous thrombosis is concerned the latency of certain types is to be borne in mind, and in diseases like chlorosis in which obscure pains in the legs may indicate deep thrombosis, careful examination should be made, and if any suspicion of involvement of the calf veins exists the patient should be kept completely at rest. In puerperal women also, and in patients who have had abdominal operations, the possibility of thrombosis and its frequent latency should be kept in mind, and complete rest, care in avoiding straining at stool, and the avoidance of sudden movements should be enjoined until the time of danger is past. In outspoken peripheral thrombosis avoidance of manipulation of the thrombosed vein by the physician, absolute rest, the avoidance of straining and coughing, and of too abrupt movements have already been mentioned, and are more fully discussed under the treatment of thrombosis.

Little can be done to prevent the occurrence of embolism in cases of cardiac thrombosis of the ordinary parietal type. As a matter of fact, the cardiac stimulation necessary in such patients may actually increase the danger of embolism and instances in which the administration of digitalis has been followed by evidence of the lodgement of emboli are by no means unknown. In acute vegetative endocarditis, measures having a sedative effect on the heart, such as the application of an ice-bag to the præcordium, render the likelihood of embolism less. The prevention of mercurial and paraffin embolism has already been discussed under those headings.

The prevention and treatment of *air embolism* requires separate discussion. Inasmuch as the danger of air embolism is greatest during operations on the neck, the surgeon should take special pains when operating in this situation to avoid wounding the large veins. This is, however, impossible in all instances, for in patients with chronic inflammatory conditions involving the deep structures of the neck the vessels are often displaced and altered in appearance, so that even the most experienced surgeon may wound them. It has been proposed by Lafargue to operate under water in such cases, but this seems obviously impracticable. It does seem important, however, to keep the wound moist, for, according to Tillmanns, air embolism only takes place when the wound is dry. If air embolism has actually occurred the surgeon, if observant, can prevent the entrance of further air by quickly placing the finger over the opening in the vessel, and if but a small amount of air has entered, this may suffice to save the patient from serious symptoms. If the patient shows marked evidences of air embolism, three methods of procedure are available: the direct aspiration of the air from the heart, forcing the air onward and getting it beyond the heart cavities and pulmonary vessels, and forcing the air in a direction opposite to the circulation out of the wound through which it entered. Direct aspiration of the right side of the heart has, so far as we know, been used only in animals. Demons and Begonin used it with some success in dogs, and its use in human beings

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is worth considering. Attempts to force the air onward may be made by introducing saline solution into the circulation through the wound in the vein, or may be brought about indirectly by attempting to make the patient cough or vomit. In some instances it has been possible to force the air out of the opening in the vein by rhythmical compression of the thorax, allowing the opening to remain open while the compression is being made and closing it at other times. As air embolism is so rapidly fatal, promptitude on the part of the surgeon is one of the chief considerations in its treatment. Without this, no treatment is of avail.

In the prevention and treatment of *fat embolism* little can be done. Inasmuch as the commonest cause is fracture of long bones, care should be taken in the treatment of such injuries to use as little manipulation as possible. In operations on the long bones also the surgeon should avoid unnecessary manipulation, and in the application of brisement forcé, especially when the large joints are involved, the danger from fat embolism should be borne in mind, and the procedure should be carried out as expeditiously as possible. The opening up of closed wounds and the ligation of vessels leading from the wound have been suggested in the treatment of fat embolism, but these procedures are little likely to lead to good results, and their application is like locking the stable-door after the horse is stolen. Attempts to emulsify the fat by the introduction of sodium bicarbonate into the circulation seem farcical considering the weak solutions which can safely be used and the tremendous dilution which must result from mixture with the blood. Efforts to dissolve the fat by the introduction of ether into the circulation must be regarded as positively dangerous considering the fact that thrombosis may be produced experimentally by the introduction of ether in this manner. After all, the most that can be done is to treat the patient expectantly, paying special attention to cardiac stimulation. There would seem to be some danger, however, in too active cardiac stimulation, for the sudden forcing of large numbers of the fat emboli through the pulmonary capillaries into the general circulation might, if Ribbert's views are correct, produce serious cardiac and cerebral disturbance from their lodgement in the vessels of these organs.

The treatment of *pulmonary embolism* has for its objects first, the support of the heart which, as a result of the shock of the embolus, is usually very much depressed, and, secondly, the prevention of the dislodgement of other emboli. Immediately after the lodgement of a pulmonary embolus active cardiac stimulation must be employed, as at this time the cardiac weakness is often extreme and may be the cause of death. The usual diffusible cardiac stimulants must be promptly employed in adequate doses. Ammonia, ether, and alcohol may be given for their immediate effects, to be followed later by digitalis, caffeine, or strophanthus. It is to be borne in mind that the object of this cardiac stimulation is to tide over the dangerous period of heart depression. When this has been done cardiac stimulants must be used with great caution, as overstimulation may lead to the loosening of other emboli from the point of origin of the first one and may cause a fatal issue. It is well, therefore, to rely upon the milder cardiac tonics, such as strychnine, and quinine, after the first cardiac depression has been overcome.

The main indication for the prevention of other emboli is absolute physical and mental rest. For this purpose morphine is generally needed at first,

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but after a few days the marked restlessness which often accompanies the lodgement of a pulmonary embolus usually disappears, and the milder sedatives, such as the bromides, are sufficient. The prevention of coughing by pulmonary sedatives and the prevention of straining at stool by keeping the bowels loose cannot be too strongly insisted upon. The rest for the first eight or ten days should be as nearly absolute as possible. After this limited movements are allowable, but the patient should remain in bed from four to six weeks, and should avoid any violent exercise for months after convalescence is established. The diet should at first be liquid, as this allows the patient to be fed with a minimum of exertion on his part. After a week or ten days a soft diet may be allowed and this may be gradually modified until the patient is on ordinary diet. Tea, coffee, and stimulants are best avoided. Pain resulting from pleurisy, and the various complications of pulmonary embolism, such as empyema and pneumothorax, are to be treated in the usual way.

The treatment of *embolism of the arteries of the extremities* has for its object the relief of immediate symptoms like pain, and the encouragement of the formation of collateral circulation. For the pain, which is frequently very severe, morphine is generally needed, and in embolism it is often necessary to continue its use for some time, for, unlike thrombosis, in which condition the pain rapidly recedes, embolism is often accompanied by an increase in suffering with the advent of gangrene. Local applications over the vessels in the form of unguentum hydrargyri, or 30 per cent. ichthyol in glycerin or lanolin, and applications of moist heat have also been recommended. In applying any local medication, direct pressure on the vessel should be avoided. Little can be done to encourage the formation of a collateral circulation unless the necessary anastomoses are present. The limb should be placed in a position which favors the flow of blood to it, moist heat should be applied to the surface, and judicious cardiac stimulation should be employed. When gangrene occurs surgical treatment is necessary. The occurrence of venous hyperæmia is to be avoided. Strict asepsis should be carried out to prevent infection of the necrotic part, and finally amputation is indicated. The amputation should not be performed until a well-marked line of demarcation has formed and the inflammation in the neighboring tissue has subsided. As in amputation for other forms of gangrene, care should be taken to make the incision through sound tissue.

The treatment of *embolism of the central artery of the retina* is unsatisfactory. It is claimed that good results have in some instances followed massage of the eyeball, the object of this being to break up the large embolus and force it from the trunk of the retinal artery into the smaller branches, where it could do less damage. The occurrence of an embolism of the retinal artery should call attention to the danger of a similar lesion elsewhere, and demands a careful examination of the patient with the injunction, if it seems necessary, of complete rest for some time.

PHLEBITIS.

Inflammation of the veins is the most common form of vascular inflammation unless, with some authorities, we consider arteriosclerosis as inflammatory in nature. The process may be acute, subacute, or chronic; may

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originate in the tissues about a vein as a periphlebitis, may begin as a lesion of the intima, an endophlebitis, or, rarely, may start in the middle or external coats of the vessel without extension from surrounding tissue.

Etiology.—Phlebitis is usually a secondary rather than a primary disease, and commonly results from trauma, from the direct extension of inflammation from a local inflammatory process, or from the metastasis of infectious or toxic material from foci of inflammation elsewhere in the body. Instances of so-called "idiopathic" phlebitis are not lacking, but here as elsewhere the term "idiopathic" indicates little but a lack of exact knowledge, and merely serves to show that the etiology of some forms of phlebitis is still obscure.

The etiology of phlebitis from trauma needs no special comment. Phlebitis resulting from direct extension is common, and occurs in connection with most local inflammations. Certain forms of phlebitis from extension are especially prominent on account of their frequence and their danger. Among these may be mentioned the septic phlebitis of the uterine and peri-uterine veins accompanying puerperal infection, the phlebitis of the prostatic veins in certain cases of gonorrhœa, the phlebitis of the veins of the intestine in appendicitis, dysentery, and hemorrhoids, the phlebitis of the cerebral sinuses which may accompany mastoiditis, and the phlebitis of the umbilical vein which occurs in the newborn. In local inflammations of the peripheral soft parts, of bones, and of other viscera than those mentioned, phlebitis also occurs, but is of less moment because less apt to give rise to severe secondary manifestations. The exciting cause of the phlebitis in most instances is naturally the same organism or organisms which caused the original inflammation. In puerperal sepsis the streptococcus is most commonly found; in gonorrhœa, the gonococcus; in appendicitis and mastoid disease, one or the other of the pyogenic cocci, often associated in the former instance with the colon bacillus.

Phlebitis of a metastatic character may accompany general sepsis, but is most frequently seen in single vessels as a complication or a sequel of the various acute infectious or toxic diseases or of certain cachectic states. Inasmuch as in most instances this form of phlebitis is accompanied by thrombosis of the affected vessel and the symptoms of thrombosis usually dominate the clinical picture, the discussion of the etiology of thrombosis contains most of the information bearing on the cause of thrombophlebitis. Reference may again be made to the commoner infections with which secondary phlebitis may be associated. Typhoid fever and puerperal fever are the most common of these conditions with us, although von Schrötter claims that complication is more frequent in smallpox. Of other acute infections in which the complication may appear must be mentioned influenza, scarlet fever, measles, erysipelas, diphtheria, tuberculosis, pneumonia, appendicitis, dysentery, gonorrhœa, and syphilis. Of late years a good deal of attention has been called to the phlebitis following surgical operations, and especially abdominal operations. The exciting cause of the phlebitis complicating these diseases is by no means clear in many instances. In individual cases bacteria have been isolated from the thrombus, but it cannot be definitely stated that the phlebitis is always of bacterial origin, and there is, in fact, some ground for believing that at times it is toxic rather than infectious. Much more bacteriological and pathological investigation is needed before the matter can be considered as settled.

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In the instances of phlebitis following anæmic and cachectic conditions and associated with gout and rheumatism the same doubt as to the exciting cause prevails. In the case of anæmias and cachexias the increased predisposition to infection produced by the primary disease is well recognized, but whilst there is some evidence that infection plays a part in producing the secondary phlebitis, it is not yet conclusive. In the case of gout and rheumatism there is, besides the general predisposition to infection, the peculiar vulnerability of the cardiovascular system which is so common in the subjects of these diseases. Here again it is not clear whether the phlebitis is due to the same poison which causes the joint lesions or whether it is due to a secondary action of bacteria or their toxins. The nature of the so-called "gouty" phlebitis has already been discussed in the article on Thrombosis, and we merely wish to emphasize here the point that the direct connection with gout is by no means proven. The same remarks apply to many cases described as rheumatic phlebitis. That phlebitis occurs in gouty and rheumatic patients is beyond question, but exactly similar types of the disease appear in those who have never had gout or rheumatism, and the relation may be merely one of coincidence.

Chronic phlebitis is usually associated with chronic inflammatory lesions in the neighborhood of the affected vein or with a condition of passive congestion. It may also be caused by the entrance of animal parasites or their ova into the vessels, the commonest and most characteristic example of this being the chronic endophlebitis caused by the bilharzia worm (*Schistosomum hæmatobium*).

In all forms of phlebitis personal predisposition must not be forgotten. There is just as much reason to believe that certain individuals have particularly vulnerable veins as that other individuals have especially vulnerable pulmonary tissue. Instances of a distinct family tendency to vascular disease, and especially to certain forms of phlebitis, are by no means rare.

Special Pathology.—The pathological picture presented by a vein which is the seat of phlebitis varies with the duration and character of the lesion. In acute phlebitis resulting from the extension of surrounding inflammation the vessel wall is usually somewhat thickened, perhaps translucent-looking and red or grayish red in color. Actual purulent infiltration of the vessel wall may be appreciable to the naked eye. On opening the vessel the lumen is found to be filled with a thrombus of the white or mixed variety which may be in a condition of purulent softening, or, if the process has lasted some time, may show signs of organization. The microscope shows in such a vein an infiltration of the vessel wall with polynuclear leukocytes, a spreading apart of groups of cells by the inflammatory exudate, an extensive destruction of the finer fibers of elastic tissue, and sometimes actual necrosis of patches of the vessel wall. In ordinary thrombophlebitis the process is similar, but the evidences of inflammation are less marked. The changes which occur when recovery takes place have already been described under organization in the article on Thrombosis. It is merely necessary to state here that so far as the vessel wall is concerned regeneration of the tissues follows the organization or absorption of the thrombus and is participated in not only by the muscle and connective tissue, but also by the elastica. In some instances acute phlebitis is not accompanied by thrombosis, and this is especially apt to be the case in certain types of phlebitis of the superficial veins.

In chronic phlebitis there is a thickening and stiffening of the vessel wall

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which may or may not be accompanied by thrombosis. This is often associated with distinct dilatation of the vessel. Microscopic examination of such a vein shows an increase in the cells of the intima which may be either diffuse or patchy, an hypertrophy of the musculature, and an increase in the connective tissue throughout all coats, but especially marked in the adventitia. There may be a marked increase in the elastic fibers of the vessel wall and the vasa vasorum may be considerably dilated and show proliferative changes in their lining endothelium.

In infection with the bilharzia the pelvic veins are involved, according to Letulle,[1] in a peculiar form of phlebitis. The venous changes in this instance are due to the lodgement of the worm in the vessels and are most likely to be found in the pericolic, the perirectal, and the mesocolic vessels. They result partly from the direct mechanical action of the worms and their spined eggs, and partly from the action of toxins secreted by the parasites. The phlebitis which results is a pure endophlebitis. The intimal cells proliferate and produce bud-like projections which invade, and sometimes completely fill, the lumen of the affected vessels. There is also proliferation of the subendothelial coat of connective tissue. This form of phlebitis is, however, never accompanied by thrombosis.

Besides these varieties there is a special type of phlebitis which has been described by Ernst Neisser[2] and by Schwartz[3] as phlebitis migrans. In this type of the disease the lesion appears to the naked eye as a fusiform swelling of the wall of the vein, sharply localized, not seriously impairing the lumen of the vessel, and not accompanied by thrombosis. Under the microscope this swelling is found to be due to the infiltration of a localized area of the outer and middle coats of the vessel, with a richly vascularized granulation tissue. In Neisser's specimens, taken from patients who had a luetic history, the collections of cells were more or less closely grouped about the small vessels, and were interspersed between areas of relatively normal tissue. In Schwartz's specimens, from patients with tuberculosis and phlebitis migrans, the cell infiltration was much more diffuse, but judging from descriptions the lesion was essentially the same.

The occurrence of specific tuberculous and syphilitic phlebitis needs only brief mention here. Tuberculous phlebitis is of little direct clinical import, though its relation to acute miilary tuberculosis of the lungs, long since established by Weigert and his pupils, renders it of great pathological significance. Syphilitic phlebitis, in the sense of an inflammatory vein lesion accompanied by specific luetic changes, occurs in the form of gumma formation in the walls of the veins. It also is of pathological rather than clinical significance. There are instances on record of an obliterative phlebitis in connection with intestinal and pancreatic syphilis which is probably syphilitic in nature, but which presents no pathognomonic histological changes. It is probable that in the near future the specific nature of doubtful venous lesions may be cleared up by finding in them the *Spirochæte pallida*. An extensive discussion of syphilitic phlebitis may be found in the monograph of Proksch.[4]

The favorite sites of phlebitis differ according to the cause. Traumatic phlebitis, the form following the infectious and cachectic diseases, and so-

[1] *Compt.-rend. de la Soc. de biol.*, 1905, lviii, 607.
[2] *Deutsch. med. Woch.*, 1903, vol. xxix, Nr. 37.
[3] *Virchow's Archiv*, 1905, vol. clxxxii, Heft 2.
[4] *Ueber Venensyphilis*, Bonn, 1898, Handstein.

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called gouty and rheumatic phlebitis usually attack the veins of the extremities, the lower extremities much more frequently than the upper, and the left side much more frequently than the right. The veins of the lower extremities are probably most frequently attacked on account of the greater chances of obstruction to the return flow of blood in them, especially in patients with feeble circulation, the greater strain to which the vessels are subjected from the action of gravity, and their greater liability to trauma. Phlebosclerosis, which is held by some authorities to predispose to attacks of acute phlebitis, is also more common in the veins of the lower extremities. The reason why the lesion occurs more frequently on the left side is not clear. There are reasons why thrombosis should be more frequent on the left side, as has already been discussed in the article on that subject, but why inflammation of the vessel, which apparently precedes the thrombosis in most instances, should generally occur on the left side has not been satisfactorily explained. Phlebitis from extension naturally occurs most frequently in those situations where acute inflammation is common, as the skin and subcutaneous tissues, the alimentary tract, and the lungs. As already mentioned, certain forms of phlebitis from extension are especially dangerous on account of their tendency to produce general sepsis or secondary phlebitis and thrombosis elsewhere.

Symptoms.—Acute phlebitis may cause both general and local symptoms. The general symptoms may precede the local ones. The patient may feel unwell, and there may be a slight fever and a gradually increasing pulse rate before any appreciable local evidences of phlebitis appear. When the phlebitis is septic in origin the fever may be intense and the illness may begin with a chill. Ordinary cases of phlebitis do not as a rule develop fever higher than 101.5° to 102° F., and this usually subsides a few days after the onset of the attack. Very often the occurrence of pain, most marked at the site of inflammation, but usually radiating more or less, is the first symptom. The symptoms and signs which develop after the first few hours depend upon the presence or absence of thrombosis. In most instances the vessel becomes plugged by a thrombus and the symptoms already described in the article on Thrombosis occur. Thrombosis does not always occur, however. It is more commonly absent in phlebitis of superficial veins than in phlebitis of deep veins. In case it is not present the inflamed portion of the vein is apparent as a semi-elastic, tender cord, the skin over which is often reddened. There is usually some local inflammatory œdema of the tissues over the vessel. The absence of thrombosis may be tested by compressing the vein at a point between the inflamed area and the heart, and determining whether the blood is dammed back by this procedure. Phlebitis of the veins of the limb is usually accompanied by a certain amount of stiffness and disability, especially if the inflamed vein be in the neighborhood of a joint. This stiffness is due to the pain which is produced by movement of the affected limb, and is not a paresis or paralysis. When thrombosis does not occur, the acute signs of phlebitis usually begin to disappear in two or three days, and by the end of ten days or two weeks the vein may have returned to normal.

The clinical picture presented by the so-called "phlebitis migrans" is a little different from that of the ordinary acute phlebitis. Phlebitis migrans may occur during the tertiary stages of syphilis or in patients who have no specific history. It attacks by preference the veins of the upper extremities,

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especially those about the bend of the elbow, both above and below the joint, and appears, not as a cord-like, uniform infiltration of a segment of a vein, but in the form of multiple spindle-shaped swellings averaging 3 or 4 cm. in length by 1 cm. in diameter. These swellings appear along the course of a single vessel or may be distributed on several vessels. They are usually somewhat sensitive to the touch, are firm but elastic, and may or may not be accompanied by evidences of inflammation of the overlying tissue. Sometimes the skin over them is pale and free from all signs of inflammatory change; in other instances it is distinctly reddened. A slight but distinct inflammatory œdema, usually pretty well confined to the region of the inflamed patch, is sometimes present. This form of phlebitis is never associated with thrombosis. The veins distal from the enlargement show no engorgement and there is no general œdema of the area supplied by the inflamed vessel. In a few instances sensory changes in the fingers, in the form of slight paræsthesia, have been described. The peculiarity of this form of phlebitis which gives it its name is the fact that the fusiform swellings on the vessels may actually move from one part of the vessel to another. It is not to be assumed from this statement that there is active or extensive motion, but measurements taken from day to day have shown that the swelling may occasionally change place to a slight extent. So far phlebitis migrans has only been observed in connection with syphilis and pulmonary tuberculosis, but as more instances are reported it will probably be shown that it is not invariably associated with these diseases.

Acute suppurative phlebitis is always accompanied by thrombosis, and besides causing the ordinary signs of thrombophlebitis, it is commonly associated with indications of a general sepsis. There may be fever of an intermittent type, chills, profuse sweats, rapid action of the heart, and the presence of a marked leukocytosis. This form of phlebitis is most common in the deeper peripheral veins, in the hemorrhoidal veins, the uterine veins, the cerebral sinuses, and the portal vein and its branches. The symptoms of the varieties of suppurative phlebitis of medical interest are considered in detail in the article on Thrombosis. Chronic phlebitis gives rise to the same symptoms as the acute variety, although their intensity is less. It is very apt to be marked by a series of exacerbations, during which the pain and symptoms of inflammation become more marked, alternating with a series of remissions. It may or may not be accompanied by thrombosis, and, just as in the acute form, the symptoms will depend to a considerable extent on this factor.

Sequelæ.—The sequelæ of phlebitis depend in the main on the presence or absence of an accompanying thrombosis. If thrombosis is absent, a complete return to normal of the vessel is frequently observed. If thrombosis is present, the element of importance is the character of the thrombus. If the thrombus is a bland one, it may be absorbed and the vein return to normal, or it may become organized and the local sequelæ of thrombosis already described in the article on that subject may be left behind. If the thrombus is septic or associated with certain diseases, as chlorosis or puerperal infection, there is considerable danger of embolism, and this is the most serious complication of phlebitis.

In certain forms of phlebitis there is a strong tendency to recurrence. This is true of syphilitic phlebitis and also of idiopathic recurrent thrombophlebitis, under which head we believe the so-called "gouty" phlebitis should

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be included. In syphilitic phlebitis the tendency is for the recurrence to attack different veins each time. In idiopathic recurrent thrombophlebitis one of the characteristic features is that the process attacks successive segments of the same vessel, usually until it has completely obliterated it.

Diagnosis.—The diagnosis of phlebitis of a superficial vein is usually a simple matter. The sudden onset with pain, the slight constitutional symptoms, and the thickened vessel with the overlying, reddened, œdematous skin leave little room for error. In some instances of thrombophlebitis there are sources of error, and these are described in the article on Thrombosis. Here also is to be found the discussion of thrombophlebitis of the veins of the different viscera and of the vessels of the different parts of the body.

Prognosis.—The prognosis of phlebitis hangs upon the concurrence of thrombosis, and depends almost entirely upon the character and location of the thrombus. For this reason it is discussed under the head of disease associations and special forms of thrombosis in the article on Thrombosis. Simple phlebitis unaccompanied by thrombosis has almost invariably a favorable outcome. The tendency of some forms to recurrence should be borne in mind in giving a prognosis.

Treatment.—The treatment of phlebitis is essentially that of thrombosis; it depends on the cause and situation of the lesion, but is mainly influenced by the fact that thrombosis is usually present. In a few forms, such as syphilitic phlebitis, specific internal treatment is demanded; but as a rule the treatment consists of relieving the pain by the methods of general and local treatment already described, and putting the patient completely at rest. The excision of the inflamed area of vein, as recommended by the French school and by Moullin, may be advisable in some cases.

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CHAPTER XIII.

THE DISEASES OF THE LYMPHATIC VESSELS.

By ALDRED SCOTT WARTHIN, PhD., M.D.

Introduction.—The diseases of the lymphatic vessels have hitherto been accorded but slight attention in works on internal medicine. In fact, in the majority of such text-books no separate treatment of this subject is deemed necessary, and only passing allusions are made to pathological conditions of the thoracic duct or peripheral lymphatics in their connection with more general pictures of disease. This is due in part to the fact that the lymphatic system, having its roots in the lymph spaces of the various organs and tissues, stands in such intimate relationship to parenchyma that pathological changes in one mean the involvement of the other, so that it becomes possible only in rare cases to separate the pathological anatomy of the smaller lymphatics from that of the organ or tissue concerned. Only in the case of the larger lymphatic channels is it more often possible to distinguish independent pathological conditions and thus to formulate an independent pathological anatomy of the lymphatic vessels.

Still more difficult has it been to separate clinically the independent conditions of the lymphatics, since the symptoms arising from these are often obscured by the broader or more striking manifestations of the associated or secondary changes dependent upon the primary lymphatic conditions. As in the case of the diseases of the bloodvessels, the morbid affections of the lymphatics so frequently lead to the involvement of the entire organism that the primary part played by them is lost sight of entirely or is thrown into the background through the overshadowing importance of the resulting organic or systemic functional disturbance. Inflammation, tuberculosis, or malignant disease of the thoracic duct may be wholly masked by the septicæmia or pyæmia, general miliary tuberculosis, or metastases dependent upon these conditions. To such an extent is this true that some writers have denied to affections of the lymphatic vessels any independent symptomatology aside from that resulting from obstruction to the outflow of lymph, such as œdema, chyluria, chylous ascites, chylothorax, chylopericardium, etc. As it is, many of these cases are relegated to surgery for final consideration, and for this reason the pathology of the lymphatics has been more adequately treated in surgical works than in those of internal medicine. Nevertheless, these cases usually come first into the hands of the physician, and for that reason a discussion of their etiology, symptomatology, and diagnosis is needed in text-books of medicine. Finally, with increasing casuistics and their careful analysis the diseases of the lymphatics must come to hold a more independent and important position. This is true particularly of the thoracic duct and its branches, the general pathology of which has been greatly extended within recent years. To experimental pathology we may look for further development in this direction.

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In the consideration of the diseases of the lymphatic system it will be found convenient to follow the natural anatomical division of the Thoracic Duct and the Peripheral Lymphatics.

1. DISEASES OF THE THORACIC DUCT.

General Considerations.—The thoracic duct is the main trunk of the lymphatic vascular system, and receives the chief portion of the lymph from the peripheral lymphatics. It is formed by the union of the lumbar lymphatic trunks (*trunci lumbales*), that convey the lymph from the lower extremities, pelvis, genitalia, and abdominal wall, with the intestinal trunk (*truncus intestinalis*), into which the chyle vessels empty. At the point of union at the level of the first or second lumbar vertebra a dilatation is usually found (*receptaculum* or *cysterna chyli*). This sac, however, is not always present, and its place may be taken by a plexus of lymphatic vessels. Passing through the aortic opening in the diaphragm, the duct ascends in the posterior mediastinum to the right of the median line, lying between the aorta and right vena azygos. At the level of the fourth dorsal vertebra it turns to the left and ascends on the M. longus colli to about the height of the sixth cervical, and, after receiving the lymph trunks from the upper portion of the body, empties into the left subclavian vein just before its union with the left internal jugular. While the above may be regarded as an average course for the duct, the degree of variation is very great, not only in course, but also as regards anastomoses and terminations.

The routine examination of the thoracic duct in autopsy work has been much neglected, owing to the prevalent mistaken idea that its demonstration is a matter of great difficulty. As a matter of fact, it is easily found. If, after the removal of the heart and left lung, the right lung is turned over into the left side of the thorax, the tissues on the right side of the posterior mediastinum and the overlying pleura are put on the stretch, and it is but rarely the case that some portion of the duct is not recognized through the delicate pleural covering or as soon as the latter has been slit longitudinally and dissected away. The greater portion of the duct can be dissected out at this time, or a thread may be tied around it to make its recognition more easy after the removal of the neck organs and thoracic vessels.

The right lymphatic duct, sometimes called the right thoracic duct, receives the lymph from the right side of the head, neck, thorax, right lung, right heart, right upper extremity, and upper surface of the liver. It is less than an inch long and empties into the right subclavian or internal jugular near their junction. Like the thoracic duct its opening has a double valve. Nothing is known of its pathology.

Anomalies.—Numerous anomalies have been described. Instead of a single duct there may be a plexus of small lymphatics extending along the entire course of the normal vessel, or the duct may be represented by two or more distinct trunks, which may run an individual course or may re-unite to form a single channel, persisting throughout the remaining portion of the course or again dividing. In the case of a double duct, one vessel may empty into the right subclavian vein, the other one into the left, or the termination may consist of a delta-like lymph plexus. Anomalies of termination are very frequent. The duct may empty into the right subclavian

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vein, right internal jugular, by two trunks into the right and left subclavians or the right and left internal jugulars, the junction of subclavian and internal jugular on one or both sides, the brachiocephalic vein, inferior vena cava, azygos major, etc. In the case of termination by plexus, the various trunks may empty into several different veins. Some of these anomalies of termination occur so often that they have been regarded by anatomists as representing normal variations. They may, however, be associated with vascular anomalies. When the thoracic duct empties into the right subclavian vein the innominate artery may be absent, the right common carotid and right subclavian springing directly from the arch of the aorta. Such anomalies are probably the result of disturbances of development of the primitive aortic arches, either with transposition of the viscera or with an abnormal origin of the large arterial trunks. The double ducts are to be referred to the persistence of the right and left primitive lymphatic channels.

The clinical significance of these anomalies is chiefly surgical. The anomalous branches may be injured by surgical procedures, particularly when the duct or ducts rise high in the neck. This occurs not infrequently in the case of a right-sided duct or a double duct. Lymph fistula or chylothorax constitutes the usual symptom. In other cases the anomalous duct or branch may be ruptured by trauma and the resulting chylothorax be regarded as a medical condition until its nature is discovered, when it may be handed over to the surgeon for final treatment.

Absence of the thoracic duct is mentioned repeatedly in obstetrical literature as a cause of *œdema neonatorum*, but authentic observations of such an anomaly are apparently wanting, and it is probable that a hypothetical cause has been passed along in the literature as a real one.

Hemorrhage.—Hemorrhage into the thoracic duct may occur as the result of trauma to the mesentery or intestines, retroperitoneal or mesenteric hemorrhages due to congenital or acquired hæmophilia (severe anæmia, chronic icterus), extreme passive congestion of the portal system in hepatic cirrhosis, ruptured sac in ectopic gestation, and following pelvic operations. In a case of fatal hemorrhage into the stomach from an œsophageal varix the intestines were filled with a thick tarry mass, while great numbers of partially disintegrated red cells were found in the radicles of the thoracic duct, partly free and partly within phagocytes. The entrance into the general circulation through the thoracic duct of a large amount of blood so changed would offer conditions favoring thrombosis and embolism in the smaller vessels of the body. No symptoms referable to a thoracic duct condition would exist unless thrombosis occurred within the duct itself or at its mouth, obstructing it so that chylothorax or chylous ascites would occur in the absence of an adequate collateral circulation. Such cases have not yet been recognized.

Thrombosis.—Thrombosis of the thoracic duct has been observed in a number of cases. Two varieties may be described. In one the thrombus begins within the subclavian vein, at or near the mouth of the duct, and finally obstructs the latter; in the other form the thrombus occurs primarily within the lumen of the duct. The cases described by Oppolzer, Cayley, Turney, and others belong probably to the first type. Oppolzer's case was one of cardiac valvular lesion. At autopsy a thrombus obstructing the mouth of the thoracic duct was found. There was neither chylothorax nor chylous ascites present. Cayley's case presented a thrombus closing the

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mouth of the duct and causing such marked dilatation of the duct and the receptaculum chyli with its radicles, that the latter could be felt as a large tumor during life. In Turney's case both chylothorax and chylous ascites were present, the duct and all its radicles being greatly dilated, while its mouth was found to be blocked with a thrombus.

Etiology.—The causes of thoracic duct thrombosis have been given by various authors as hemorrhage into the duct, inflammation of its wall, trauma, tuberculosis, metastasis of malignant tumors, infection, presence of filariæ, pressure of neighboring tumors, aneurisms, anomalous vessels and exostoses of the vertebræ, the obliteration of the left subclavian vein, etc. Those occurring primarily in the vein at the mouth of the duct may be dependent upon a valvular lesion, or they may be infective. Carcinomatous thrombi may also have their seat at the mouth of the duct. There can be but little doubt that some of the so-called thrombi found within the thoracic duct were tubercles or tumor-masses.

Symptoms.—The symptomatology of thoracic duct thrombosis is purely one of obstruction in so far as its distinctive features are concerned. Chylous ascites alone or combined with chylothorax or chyluria would point to such an obstruction. The dilated receptaculum might be palpable through the abdominal wall as an elastic retroperitoneal tumor. Aspiration of such a tumor should be practised, as it might lead to a definite diagnosis of obstruction of the duct from the character of the fluid obtained. Obscure abdominal pains, intestinal disturbances, œdema or elephantiasis of the external genitals or lower extremities may occur as features of the clinical picture.

The occurrence of symptoms of obstruction, as well as their severity, will depend upon the adequacy of the collateral circulation. A thrombus located at the mouth of the duct is more likely to cause obstruction to the lymph outflow than one located nearer to the receptaculum; but, even in the former case, an anomalous termination may be able to compensate fully, and symptoms of obstruction may be wholly wanting. A thrombus slowly formed, or one that only partly blocks the lumen, is not likely to cause any symptoms of obstruction.

The thrombus may undergo simple softening, and finally disappear entirely. One case, at least, has been reported of the organization of the thrombus and the permanent obstruction of the lumen of the duct by a mass of newly formed connective tissue canalized by new blood and lymph vessels. Calcification of the thrombus may take place, leading to the formation of a thoracic duct stone. The "chyle stone" occurring in the receptaculum, described by Scherb in 1729, is an interesting pathological finding, and probably represents an old thrombus that had become calcified.

Inflammation.—A number of cases have been described; in the majority it has been purely secondary to inflammatory processes involving the chyle vessels and the pelvic radicles. In dysentery, suppuration of the mesenteric glands, pelvic suppurative processes, etc., the entrance of bacteria into the mesenteric and pelvic lymphatics is probably the rule, but in the majority of cases they appear to pass on with the lymph into the blood stream without causing local lesions in the duct or its radicles. It is not improbable that the thoracic duct becomes the most important portal of entrance into the blood stream of pyogenic organisms coming from local lesions in the territory drained by it. It plays, therefore, a very important role in the

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causation of pyæmia and septicæmia. The metastatic abscesses occurring in dysentery may well owe their origin to a transportation through the thoracic duct. Likewise, the entrance of gonococci into the blood stream may occur chiefly through the thoracic duct, as it is now known that the gonococci gain entrance to the lymphatics of the genitals and pelvis. In some cases the walls of the duct may become the seat of a purulent inflammation, and at autopsy its lumen may be found to contain pus. Such cases have been mentioned or described by Adams, Worms, Andrals, Gendrin, Enzmann, Schweninger, and others. The independent nature of the thoracic duct suppuration is not clear in any one of these cases.

In a case seen by the writer of purulent salpingitis occurring in a young girl convalescing from smallpox, the pelvic and mesenteric lymphatics were the seat of a marked suppurative inflammation, the receptaculum and the thoracic duct being similarly involved. All the organs contained pyæmic abscesses. Aside from the high leukocytosis (70,000), there were no symptoms that could have been connected with the thoracic duct involvement.

Few observations exist of independent inflammation of the duct. Enzmann gives 6 cases as representing this condition, but the evidence is unsatisfactory. De Forest[1] has recently reported at length a case of *purulent inflammation of the duct*, apparently primary in character. The patient, who had shortly before had an attack of "ptomaine poisoning," became ill after partaking heartily of "cold-storage poultry," and developed nausea, followed by chills and fever, passing finally into a condition resembling typhoid fever, death taking place on the twenty-fourth day. At the autopsy no evidences of typhoid fever were found, but the thoracic duct was distended to the size of a bologna sausage and filled with foul pus of a bluish-color. (See Plate II.) The constrictions at the valves gave it a peculiar sacculated appearance. Pressure upon the duct caused pus to trickle slowly through the terminal valve into the vein. The mesenteric glands, particularly those near the duct, were enlarged. No primary purulent process was found in the intestine or elsewhere, and there were no metastatic abscesses. Cultures were not made, but from the character of the pus the *B. pyocyaneus* was supposed to be present. The kidneys showed a marked degenerative nephritis.

The clinical symptoms of this interesting case were those of a septicæmia, passing into a typhoidal state. The positive evidences of typhoid fever were lacking; and two symptoms were present that in the light of the autopsy findings might be regarded as pathognomonic. The extremely high leukocytosis, the white cells before death reaching nearly 200,000, and the rather unusual production of nausea whenever the patient was turned upon his side were the only clinical features that can be taken to form a basis for a differential diagnosis. The sausage-like tumor might possibly have been felt by deep palpation, particularly if the patient had been put into a warm bath. Otherwise the clinical picture appears to be that of a septicæmia of unknown origin.

It is probable that the condition described in 1831 by Nochher as a "gangrenous thoracic duct," which was found at autopsy a few hours after death in a patient dying of a "malignant epidemic fever," may have been similar to de Forest's case. Other cases of the same nature may exist and

[1] *New York State Journal of Medicine*, September, 1907.

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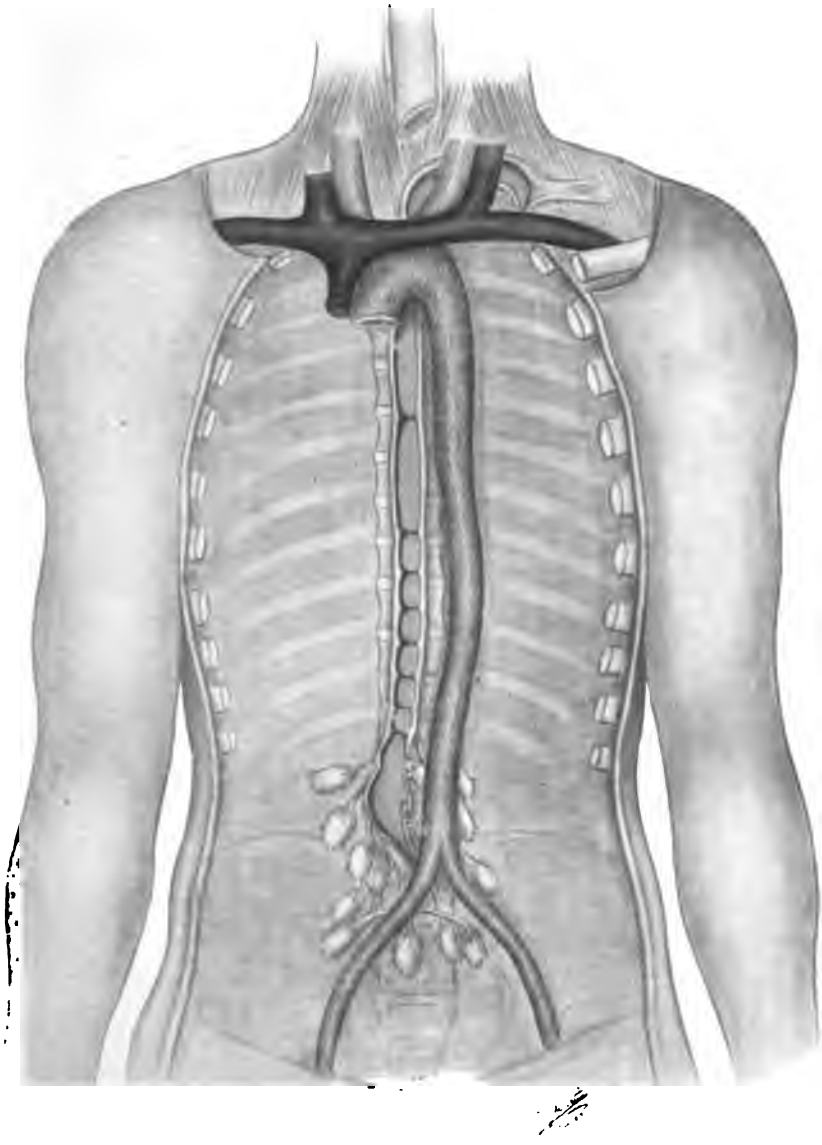
PLATE II



Acute Primary Suppurative Inflammation of the Thoracic Duct. (De Forest.)

(Bacillus pyocyaneus.)

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go unrecognized, either through the failure to perform an autopsy or because of an incomplete examination. The clinical diagnosis of such a condition has never been made up to the present time. In the case of a septicæmia or toxæmia of unknown origin, a progressively increasing leukocytosis up to very high counts might direct suspicion toward the thoracic duct as the seat of a purulent inflammation. The symptom of nausea mentioned above may be found to have some worth. Deep palpation with the patient in a warm bath should be tried. In the case of a localized abscess, involving some portion of the duct, the symptom of chylothorax or chylous ascites may be added. Finally, an exploratory operation might settle the matter and serve as a therapeutic measure in those cases in which the receptaculum or the abdominal portion is involved.

Chronic inflammation of the thoracic duct has been described in the literature. Andrals mentions a constriction of the lumen of the duct by a formation of scar-tissue in its wall at the level of the fifth dorsal vertebra. Heller found in a woman, fifty-six years old, who had suffered from ascites and marked œdema of the pelvic tissues, that the wall of the duct was greatly thickened and its lumen almost obliterated. He regarded the condition as the result of a chronic inflammation of the wall of the duct. Other similar cases of supposed chronic lymphangioitis of the duct have been reported, but it is clear from the descriptions that the condition was one of tuberculosis or infiltration of the wall of the duct by a malignant neoplasm. Thus the case reported by Schweninger, of *lymphangioitis proliferans* of the duct was undoubtedly one of carcinomatous infiltration. Likewise, the classical cases of Cheston and Assalini, in which the duct was filled with bony masses, have been passed along in the literature under the terms "calcification," "ossification," and "*lymphangioitis ossificans*" of the duct. Certainly, the description given by Cheston leaves no doubt that the duct had been invaded by an osteosarcoma primary in the pelvis. Inflammation of the thoracic duct due to syphilis, parasites (*filaria*), etc., is hinted at in the literature, but the actual pathological demonstration remains for the future.

From the few, and, on the whole, unsatisfactory, reports it will be seen how meagre is our knowledge of thoracic duct inflammation, and how great is the need for more careful clinical and pathological studies of cases of obscure septicæmia or pyæmia.

Tuberculosis.—The thoracic duct is the most important channel by which great numbers of tubercle bacilli are rapidly disseminated throughout the body, and it, therefore, is the chief avenue concerned in the production of acute general miliary tuberculosis. The duct itself may be the seat of tuberculous lesions, from which the bacilli are carried in great numbers by the lymph into the general circulation; or the duct, while in itself not affected, may be the avenue through which great numbers of tubercle bacilli, given off from a tuberculous lymph node, may pass with the lymph into the blood stream. Further, a subacute or even chronic tuberculosis may result when a small caseous tubercle occurs in the duct, giving off from time to time into the lymph stream a small number of bacilli.

Tuberculosis of the duct itself was first discovered in 1798 by Astley Cooper, who correctly described and interpreted the condition. In 1877 Ponfick pointed out the special importance of thoracic duct tuberculosis in its relation to a sudden generalization of the tuberculous process, and in the following year Weigert reported similar cases and expressed his views con-

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cerning the pathogenesis of acute miliary tuberculosis, to the effect that this condition depends upon the existence of an older tuberculous focus in the wall of a vein or large lymph duct from which the "poison" gained entrance into the general circulation. This was before the discovery of the tubercle bacillus. In 1884, Koch confirmed Weigert's views and demonstrated the dissemination of tubercle bacilli from such foci. Since then numerous observers have reported the occurrence of tubercles in the thoracic duct in cases of acute miliary tuberculosis. The more carefully a series of cases of this condition has been studied at autopsy the higher the percentage of thoracic duct lesions discovered. In a series recently reported by Longcope the duct was affected or contained tubercle bacilli in over 79 per cent. of cases of acute miliary tuberculosis. Whipple has also recently reported a series of cases in which smears made from the contents of the duct showed the presence of tubercle bacilli in all cases in which the mesenteric glands were involved. Tuberculosis of the thoracic duct cannot, therefore, be regarded as a rare condition, and its relation to general miliary tuberculosis is more important than tuberculosis of veins and arteries. Further, both clinical and experimental evidence show that tubercle bacilli may pass into the thoracic duct through an intestinal wall showing no tuberculous lesions. The views held by von Behring and Calmette as to the intestinal route of tuberculous infection emphasize the great importance of the thoracic duct as a great highway of bacillary transportation.

The infection of the duct takes place usually from caseous mesenteric, retroperitoneal, or mediastinal lymph glands, although it is possible that in some cases tubercle bacilli pass through the intestinal wall without causing lesions and into the lymphatics to excite first within the thoracic duct the characteristic lesions of the disease. Ordinarily, however, the thoracic duct lesion is secondary to an older tubercle of a lymph node.

The character of the lesion within the duct may vary greatly. There may be scattered miliary or submiliary nodules, multiple or single in the intima of the duct, or the entire wall may be studded with larger conglomerated polypoid tubercles. Caseous ulcers may be present, particularly upon the valves. In many cases there is a single large caseous nodule near the upper end of the duct, but sometimes in or near the receptaculum. In advanced cases the wall of the duct throughout its entire length may be thickened and caseous, the lumen in part obliterated or in part varicose, and in the latter case filled with a caseous or whey-like substance. Tubercles forming behind a valve flap may push the flap out into the lumen, and so obstruct the latter. Chylous ascites and chylothorax may result from tuberculous obstruction of the duct, but this is rare, an adequate collateral lymph circulation usually being developed. Except for such symptoms of lymphatic obstruction, tuberculosis of the duct gives rise to no definite clinical picture.

Syphilis.—Gummatous lesions of the thoracic duct or lesions of other nature definitely ascribable to syphilis have apparently not yet been observed.

Ectasia.—Dilatations of the thoracic duct are not uncommon. They have been reported in the literature under various heads—aneurism, varicosity, cysts, etc. The duct may be dilated as a whole or in part. The nature of some of these localized dilatations is not at all clear. In part they appear to be the result of obstruction, either from within (thrombus, tubercle, carcinoma) or from external pressure upon the duct (tumor, aneurism, etc.). When the obstruction occurs at the upper end the entire duct may be

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dilated, presenting sausage-like sacculations, while the receptaculum is as large as a hen's egg, or even larger. In other cases no obstruction is present, and there is no evidence of pressure from within or without. On the other hand, in many cases where there is actual obstruction of the duct, no dilatation of the duct occurs. By some writers the cause of the partial dilatations or varicosities occurring without obstruction is sought in a local weakening of the wall of the duct, due to defective development or to atrophy, the dilatation so formed being comparable to that occurring in arterial and venous aneurisms.

There is no symptomatology, or, in the event of rupture or obstruction, an associated chylothorax, or chylous ascites or chyluria, calls attention to the thoracic duct. The cystic enlargement of the receptaculum may be seen or palpated as a fluctuating retroperitoneal tumor, the contents of which may be recognized on aspiration.

Chyle Cysts.—The cystic dilatations of the radicles of the thoracic duct deserve special mention, because of their not infrequent occurrence and their clinical importance. They may occur as the result of obstruction to the duct or of its branches, as the result of local inflammation, or partake more of the nature of tumors. They are classed by different writers partly as *lymph cysts* and partly as *cystic lymphangiomata* or *chyle angiomata*. They may be solitary or the peritoneum may be studded with them. They vary in size from that of a pea to a man's head, are often pedicled or clustered like a bunch of grapes, and usually possess very delicate thin walls. Their contents are whitish, creamy, or, more rarely, caseous. In the large ones the fluid may be clear and several liters may be present. In cases of chyle stasis the entire peritoneum is sometimes dotted with small whitish points, corresponding to small dilatations of the chyle vessels. The intestinal folds and villi may also be studded with them. When lying close together the appearance presented is that of a lymphangioma. Small, isolated chyle cysts of this type are not at all uncommon, and are probably due to some local obstruction of a chyle radicle. The multiple lymph cysts are usually associated with a chronic peritonitis. The larger tumors are more rare and are apparently independent of inflammatory changes. They may be found even in children, and are probably to be classed with the tumors. They usually lie behind the stomach or an intestinal coil, the percussion tone over them often being tympanitic. In some cases the stomach or intestine may be pressed so closely against the abdominal wall that only a dull percussion note is obtained and the compressed stomach or intestine may be injured by aspiration or operation. The points of differential diagnosis are: the presence of a fluctuating retroperitoneal tumor, its location and relations, the character of the fluid obtained by aspiration, etc. The symptoms are wholly those of pressure.

Obstruction.—Obstruction of the thoracic duct may be caused by thrombosis, tuberculosis, metastatic tumors, inflammation, parasites within the duct, compression of the duct by diseased lymph glands, aneurism, neoplasm, exostoses and scar tissue, inflammatory constrictions of the duct, thrombosis of the subclavian or innominate vein, high venous pressure in cases of tricuspid insufficiency, etc. The effects vary greatly in different cases; when in the lower part of the duct an adequate collateral circulation is usually established without much damage resulting. Even with an obstruction of the terminal portion of the duct some cases may present no symptoms.

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In all cases in which the collateral circulation is inadequate there results a chyle stasis, with dilatation of the duct and its radicles. The chyle may escape from the distended vessels by transudation or rupture, and may infiltrate the tissues or collect in the serous cavities, giving rise to a chylothorax, chylopericardium, or a chylous ascites.

Rupture.—The thoracic duct may be torn or ruptured through trauma or surgical operation, or as the result of distention following obstruction, erosion by aneurism or tumors, etc. Numerous cases have been reported. The deep situation of the duct protects it from trauma, but laceration has followed shot and stab wounds, fracture of a rib, severe straining or coughing, severe blows upon the abdomen, crushing of the thorax or abdomen, etc. In surgical operations upon the cervical region the duct may be wounded, and this is particularly likely to happen when the duct runs high into the neck. The removal of the lower cervical lymph glands for tuberculosis or neoplasms and the complete operation for removal of carcinoma of the breast are the operations most frequently followed by evidences of injury to the thoracic duct. In the operative cases the injury may be noticed at the time of the operation or not until the dressing of the wound. There may be a distinct gush of milky or serous fluid, or such a fluid may slowly collect in the wound or dressings. In the case of an internal rupture, the condition becomes revealed through the development of a chylothorax or chylous ascites.

The rupture of the duct is fatal in some cases, as the result of a rapidly developing marasmus following the loss of large quantities of chyle. Some cases heal spontaneously. Others recover after packing of the wound or ligation or suturing of the duct.

Tumors.—Primary tumors of the thoracic duct have not yet been observed. Secondary tumors, particularly carcinoma, are not infrequent, and there can be but little doubt that in the generalization of carcinomata located primarily in the abdomen or pelvis the thoracic duct plays as important a role as that performed by it in the dissemination of tuberculosis. In the case of such transportation of carcinoma cells the duct may remain free itself, or may contain thrombi or tumor cells, or its walls may present carcinomatous infiltration.

Mature Connective-tissue Tumors.—No positive demonstration of the occurrence of these in the walls of the duct has yet been given. The *osteomas* and *chondromas* found metastatic in the duct were undoubtedly sarcomatous in nature. The *cystic* or *cavernous chylangiomas* or *lymphangiomas* have been mentioned above under Cysts. As stated there, the true nature of the cystic formation is not yet clear, and there is some doubt as to whether they should be classed with the neoplasms.

Sarcoma.—But few cases of metastatic sarcoma of the thoracic duct have been reported, and there exists no authentic observation of any primary sarcoma of its walls. Rust, in 1815, and Otto, in 1824, saw metastatic sarcomas in the thoracic duct, the primary tumor in each case being located in the testis. Winkler, in 1898, found secondary nodules in the thickened wall of the duct in a case of primary mediastinal sarcoma. The writer has seen two cases of metastatic sarcoma in the thoracic duct. In one case there was a sarcomatous teratoma of the testis, and in the receptaculum chyli a sarcomatous nodule of the size of an English walnut, completely occluding its lumen, was found. Chylous ascites was not present. In the

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second case (recently reported by Dock[1]) chylous ascites and chylothorax were present in a case of *lymphocytoma* (*lymphosarcoma*) with lymphocythæmic blood, although the total number of the white cells was not greatly increased. Occupying the root of the mesentery a large nodular lymphoid tumor was found sending up into the thoracic duct a solid cord of tumor tissue completely filling its lumen and projecting above into the left subclavian vein (Fig. 54). The walls of the duct were in part adherent to the mass and infiltrated with tumor cells. A case much resembling this one was reported by Herzog in 1899.

As stated above, it is very probable that the cases of "ossification of the thoracic duct" reported over a century ago by Cheston and Assalina were in reality metastatic *osteo-* or *chondrosarcomata*. This seems very clear in Cheston's case, in which there was a large tumor in the pelvis consisting of cartilage and bone. A mass of similar substance extended the entire length of the thoracic duct, completely blocking its lumen, but apparently not involving its walls. A smaller mass of the same substance was found in the vena cava.

FIG. 54

Lymphosarcoma of receptaculum chyli and thoracic duct, seen from behind. Case of chylous ascites and chylothorax.

Primary *endothelioma* of the peritoneum reaches the thorax through the thoracic duct and involves the walls of the latter.

From the few reports found in the literature it would seem that secondary sarcoma of the thoracic duct is most likely to occur in cases of primary sarcomatous tumors of the testis, lymphocytoma of the mesentery, osteo- or chondrosarcoma of the pelvic bones, and primary endothelioma of the peritoneum.

Carcinoma.—Secondary carcinoma of the thoracic duct is not infrequent, and a fairly large number of cases has been reported since the first one seen by Astley Cooper in 1798. Schwedenberg has pointed out the great importance of the thoracic duct as the chief channel by which carcinoma cells pass from the abdominal and pelvic organs into the lungs and the systemic circulation. Actual tumor development within the duct or in its walls is not a necessary feature of such a transportation; it may occur without any involvement of the duct itself.

[1] *American Journal of the Medical Sciences*, 1907.

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Of the 26 cases of secondary carcinoma of the duct collected by Winkler, the primary growth was in the stomach in 10 cases, in the uterus in 8, gall-bladder in 3, and 1 each in the testis, pharynx, ovary, adrenal, and kidney In all of these cases secondary nodules were present in the mesenteric or retroperitoneal glands. In the 12 cases recently reported by Schwedenberg 4 cases were primary in the uterus, 3 in the stomach, 2 in the rectum, and 1 each in the kidney, colon, and mamma. In the last case the duct was involved through retrograde metastasis.

The appearance of the duct when it is the seat of secondary carcinoma varies greatly. To the naked eye there may be no evidence of the presence of tumor cells. Small nodules, barely palpable, may be present in the wall, or the lumen of the duct may be closed by larger masses. At other times the duct may be of the size of a finger throughout its entire length, and completely filled with tumor masses. A sacculated appearance is produced by the growth of nodules behind the valves. The lumen may be completely or partially obstructed, or the cancer mass within the lumen may be recanalized. In some cases the tumor mass is larger in the receptaculum and tapers off above. The lymph glands lying along the thoracic duct may contain secondaries when the duct itself shows no involvement, and, macroscopically, it may be difficult to say whether the latter is carcinomatous or not. The enlarged chain of lymph glands should not be mistaken for a diseased duct.

When examined microscopically the duct may be found to contain free carcinoma cells or masses of these. In the majority of cases thrombi are associated with the latter, and such carcinomatous thrombi are usually situated behind the valve. They are also found at the point where the duct crosses the aorta. With the growth of the tumor cells the thrombus may become organized and adherent to the vessel wall. The latter, in turn, becomes infiltrated with the tumor cells, and the inflammatory reaction dependent upon this appears as a diffuse thickening of the wall of the duct (endolymphangitis carcinomatosa). Such an inflammation and tumor infiltration may extend from the duct into the subclavian vein (endophlebitis carcinomatosa).

The only symptoms of secondary malignant disease of the thoracic duct that can be recognized clinically are the results of the obstruction of the duct, viz., chylothorax, chyluria, or chylous ascites. The occurrence of these conditions is dependent, however, wholly upon the inability of the collaterals to take care of the lymph stasis, and in the case of an abundant anastomosis they may be absent. The tumor masses in the receptaculum chyli may reach such a size that they can be palpated.

Parasites.—Cysticerci and filariæ may occur within the thoracic duct and obstruct its lumen, giving rise in some cases to chylothorax and chylous ascites, but more often to chyluria. Thrombosis of the duct may occur as the result of the presence of the parasites and the inflammatory changes set up by them in the wall of the duct.

Symptoms and Diagnosis of Thoracic Duct Disease.—A cystic fluctuating retroperitoneal tumor, containing chyle, as shown by aspiration, and located in the region of the receptaculum chyli, points to a dilatation or cyst of the duct or its radicles.

Symptoms of sepsis or pyæmia, with a very high leukocytosis and an elongated tumor palpable in the region of the receptaculum chyli, indicate a purulent inflammation of the duct.

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Chylothorax and chylous ascites are the cardinal signs of an obstruction or rupture of the duct. Chylopericardium, chyluria, œdema of the pelvic tissues and genitalia may be associated with the other two.

Chylous Ascites.—Milky or opalescent fluids are not infrequently seen in cases of ascites. Some of these correspond so closely to chyle in their physical and chemical qualities that one has no hesitation in applying to them the term *chylous*. In other cases the lactescent fluid has been found to differ somewhat from chyle, and to such the term *chyliform* has been applied. Still more rarely—in fact but one case of the kind has been reported—a milky fluid containing neither fat nor granules occurs, a *lactescent, non-chylous* effusion. Since the character of the last named could easily be ascertained by examination, the diagnostic problem of chief importance is the distinction between chylous and chyliform fluids. At the beginning it may be said that some writers believe that such a differential diagnosis cannot be made from the physical and chemical characteristics, since fluid in all respects resembling chyle is found in pathological conditions of the peritoneum in which no lesion or obstruction of the thoracic duct can be ascertained. Various authors also hold that the only distinction between *chylous* and *chyliform* fluids is one of dilution or mixture, in the latter case with serous fluids of inflammatory origin. According to some, the term chylous should be used only when a definite lesion can be found in the lymphatics; in chyliform or adipose ascites, the lymphatics must present no abnormalities of any kind. The question under consideration, viz., the differential diagnosis of thoracic duct lesions through the character of the fluid aspirated from the peritoneal cavity, demands some criterion by which a chylous fluid may be told from a chyliform effusion in which the milkiness is due to the presence in a serous fluid of endothelial, pus, or tumor cells undergoing or having undergone fatty degeneration. Such fluids have been found in peritoneal tuberculosis, carcinoma, sarcoma, hepatic cirrhosis, cardiac lesions, chronic peritonitis, lipæmia, etc.

The character of the fluid will decide promptly in some cases. If it is white, with numerous fat-droplets present, and forming a creamy layer on standing, and if, in addition, it contains more than 0.02 of sugar, the fluid may safely be regarded as chylous and as coming from the lymphatics. The microscopic examination of the sediment may in some cases reveal the cellular origin of the fat, but usually no trace of the cells can be seen. The absence of conditions favoring the formation of a chyliform or adipose ascites adds to the strength of a conclusion as to its chylous nature.

Cases will arise, however, in which there will be great difficulty in deciding whether to call an effusion chylous or chyliform. A large amount of fat and a relatively high percentage of sugar may be found in chyliform effusions when no lesions of the thoracic duct or chyle vessels can be demonstrated. It is possible that some of these fluids resembling chyle were in reality a diluted chyle, and it is highly probable that a diapedesis of chyle may take place into the peritoneal cavity through the walls of distended chyle vessels without any actual rupture.

If chylothorax is present also, the probabilities of a thoracic duct lesion are made much greater. The sudden development of anorexia, anæmia, and emaciation are also regarded as symptoms favoring the existence of obstruction or a rupture of the duct. If the chylous fluid returns quickly after its removal by tapping, the probabilities are that a chyle fistula is

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present. In spite of these distinctions, cases of milky ascites apparently occur in which, even at autopsy, it has been impossible to say whether the effusion was chylous or chyliform.

Chylothorax.—The same difficulty exists in the case of a milky fluid in the pleural cavity, and the two forms, chylous and chyliform effusions, are likewise distinguished here. The former occurs in the event of distended or ruptured lymphatics; the latter is found in the case of the fatty degeneration of tumor, pus, or endothelial cells, in secondary carcinoma of the pleura, tuberculous and non-tuberculous pleuritis, pulmonary abscess, lipæmia (?), etc. It is a relatively rare condition, and the majority of cases of lactescent pleural effusion are instances of chylothorax, and point to lesions of the thoracic duct. The same differential points hold good as for chylous ascites.

Chylopericardium.—Milky effusions into the pericardial sac are still more rare. Both chylous and chyliform fluids have been described; in one case the chylous fluid came from the rupture of a lymph vessel, in another the chyliform fluid was regarded as a transudation from a chyliform effusion present in the left pleural cavity. The significance of chylopericardium in thoracic duct disease is the same as that of chylous ascites.

Chyluria.—The presence of emulsified fat and albumin in the urine gives it the appearance of chyle. Sugar is but rarely present. The appearance of chylous urine is very characteristic; it closely resembles milk, but usually contains pinkish coagula. Sometimes the entire urine coagulates on standing, or it separates into an upper creamy layer and a lower bloody stratum. Chyluria may be brought about by any obstruction to the thoracic duct, whether due to thrombosis, tumor metastases, tuberculosis, external pressure, filariæ, etc. By far the most common cause of chyluria is the obstruction of the duct by either the adult or embryonic form of the *Filaria sanguinis hominis*. In northern latitudes chyluria occurring in individuals who have not been in tropical or subtropical countries is due to some other form of obstruction of the duct.

As a symptom chyluria is usually intermittent, being dependent upon the position of the body, character of the food taken, digestion, amount of fluid taken, exercise, etc. In rare cases chyluria may appear during childbirth and gradually cease after delivery, to return again during the next parturition. Such cases may be explained as due to temporary lymph stasis. Symptoms of pain in the back, groin, perineum, or testicles may accompany or precede the appearance of the chyle in the urine. When the chyluria persists over a long period of time the patient may become greatly anæmic and emaciated, and finally die of exhaustion.

Serous or *chylous œdema* of the pelvic tissues, abdominal wall, genitalia, legs, etc., *lymph scrotum*, *lymphocele*, *chylocele*, *elephantiasis*, etc., are also conditions pointing to obstruction of the thoracic duct.

Prognosis.—This is dependent wholly upon the nature of the obstruction. It is favorable only in those cases in which the cause can be removed, or, the cause being non-malignant, the lymphatic circulation can again be restored through recanalization of a thrombus, establishment of adequate collaterals, etc. Filarial obstruction is rarely cured, but the patient may live many years in spite of it, unless the amount of chyle lost is very great and the drain persistent.

Rupture of the thoracic duct in the cervical region is given at the present

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time a good prognosis, as the wound may heal spontaneously or surgical treatment result successfully. Spontaneous healing of rupture of the duct in the thoracic or abdominal cavities also takes place. In some cases, in spite of surgical treatment, the patient rapidly becomes emaciated and dies from exhaustion. In general, it may be said that the prognosis in cases of thoracic duct disease with symptoms of obstruction is grave.

Treatment.—The physician's part in the treatment of disease of the thoracic duct is largely confined to symptomatic measures. His function is in the majority of cases the diagnosis of the condition and the preparation of the patient for the surgeon, in case he considers surgical interference justifiable. Beyond the first diagnostic aspiration, tapping should not be carried out except as a final necessity, since the loss of large quantities of chyle weakens the patient. Peritoneal absorption of the effusion should be permitted as much as possible. The food should be concentrated, and a diet easily digested and absorbed by the stomach should be advised. The amount of fluid taken should be restricted. In the case of filariasis, therapeutic measures directed against the parasite should be carried out. In the majority of cases the ultimate treatment of thoracic duct disease becomes surgical.

2. DISEASES OF THE SMALLER LYMPHATICS.

General Considerations.—The lymphatic capillaries consist of a simple endothelial tube. The system is believed to be wholly a closed one, and an open communication of the lymph capillaries with the so-called "tissue spaces" is now doubted by the majority of writers. The intimate relationship of the smaller lymphatics to the tissue parenchyma is such that a clinical separation of diseases of the former from those of the latter is well-nigh impossible. The larger lymphatic vessels have distinct walls, somewhat resembling those of the veins, but in the arrangement of the elastic tissue more like the smaller arteries. In the larger trunks an inner and outer elastic limiting membrane may be distinguished. The larger vessels possess numerous valves. Even in the case of the main lymphatic trunks only a limited number of clinical and pathological conditions can be separated as independent affections. Of these, inflammation, ectasia, and tumors constitute the most important.

Lymphangitis.—*Simple acute lymphangitis* is a very common affection. It occurs most frequently in association with infected wounds of the hands or feet, and is usually due to streptococci, although staphylococci, gonococci, and pneumococci may be found at times. The bacteria either pass directly into the lymph vessel from the infected wound or invade the wall of the vessel from without. Wounds received during surgical operations or autopsies, infected "hang-nails," corns, cryptogenic infections of the hair follicles, etc., are among the most common forerunners of lymphangitis; but localized inflammation of the lymphatics independent of any primary focus of infection is far from uncommon. Such forms of lymphangitis are found particularly about the lips, nose, mouth, throat, penis, and vulva.

The majority of the above forms of lymphangitis are frankly surgical, and their thorough consideration is out of place in a work on internal medicine. Nevertheless, lymphangitis as a secondary phenomenon or complication

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plays a part of practical importance in general medicine. It occurs not infrequently during the course of the acute infectious diseases, particularly in scarlatina, smallpox, measles, diphtheria, chickenpox, etc. It is frequently associated with herpes. In some individuals severe colds are preceded or accompanied by a localized lymphangitis of the lips or nostrils that may or may not go on to the development of herpetic lesions. Erysipelas is frequently complicated by a typical lymphangitis so marked as to deserve special attention. Of the chronic specific infectious diseases, gonorrhœa, syphilis, and tuberculosis are especially likely to show an incidental lymphangitis, due, however, to the specific agent of infection rather than to a secondary pyogenic infection. Lymphangitis is a constant feature of bubonic plague. Other forms of lymphangitis coming within the province of internal medicine rather than of surgery are those arising after Röntgen irradiation, sunburn, contact with poison ivy or sumach, bites and stings of insects, etc.

Pathology.—Three forms of acute lymphangitis occur—*simple*, *purulent*, and *proliferative*. In the simple form the wall of the lymphatic and the tissue immediately about it (perilymphangitis) are hyperæmic, œdematous, infiltrated with cells, and may present small hemorrhages. The wall becomes thickened, the endothelium swells, and comes to resemble epithelium. It may become necrotic and desquamate, or it may manifest proliferative activity. Coagulation of the lymph within the vessel may occur (thrombolymphangitis), or it may remain fluid. After the cessation of the cause of the inflammation the exudate may be quickly absorbed, and with the regeneration of the damaged endothelium the normal conditions are restored. A persistence of the exciting cause may lead to a chronic process.

In the *purulent* form there is a marked thickening of the wall of the lymphatic due to a purulent infiltration. The endothelium is swollen or desquamated, and the lumen becomes filled with pus or with a fibrinopurulent mass (purulent thrombolymphangitis). The collection of pus in the lumen in the intervals between the valves gives a beaded appearance to the inflamed lymphatic. Suppuration may occur and the vessel be completely destroyed at the site of the process, so that the vessel enters into an abscess cavity. An extensive phlegmonous process may be set up in the neighboring tissues. As the result of the transportation of bacteria to the regional lymph glands, secondary abscesses are produced in the latter, and a condition of general septicopyæmia may result.

An acute *proliferative exudative endolymphangitis* occurs in gonorrhœa, and is usually associated with a perilymphangitis. The lymphatic vessel becomes greatly thickened and its lumen gradually obliterated by a fibroblastic proliferation of its walls. The endothelium may also proliferate. The wall of the vessel and the surrounding tissues show areas of infiltration with mononuclear cells, plasma cells predominating. The gonococci can be demonstrated in the lymphatic vessel and in the tissues outside. Similar acute proliferative forms of lymphangitis may occur in the case of other infections, particularly in syphilis.

Symptoms.—The symptoms of acute simple lymphangitis are a localized area of redness and swelling, œdema, a painful feeling of tension, pain on movement, etc. The inflammation advances from the periphery, and as a new area becomes involved the one first affected loses its redness and swelling. When a large lymphatic trunk is involved the course of the vessel is

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shown by a wavy red line extending up the limb, slightly elevated above the surface, having a slightly beaded, cord-like feel, and very painful on pressure. In severe cases the line of inflammation may be an inch or so broad; in slight cases the red lines are very narrow. When the deep lymphatic vessels are alone involved the only sign present may be that of tenderness on deep pressure. The lymph-glands are swollen and painful, and the portion of the limb below the seat of inflammation may become œdematous. A varying degree of fever accompanies simple lymphangitis.

In the case of purulent lymphangitis the local and general symptoms are much more severe. The reddened cord-like swelling is more marked and more distinctly beaded. Pressure is much more painful. Small abscesses may form along the vessel as well as in the regional lymph glands, or the entire lymphatic may suppurate. An extensive phlegmonous infiltration may then result, or a large abscess cavity may be formed. Extensive œdema of the region drained by the affected lymphatic may develop. The general condition is worse, the fever is usually high, the pain severe, and there is marked prostration. Chills and sweating may alternate in the early stages. The final picture is often that of a septicopyæmia.

The chief symptoms of the proliferative form of lymphangitis are the thickening of the lymphatics and the development of a marked local œdema. Otherwise the clinical picture is similar to that of the other forms, although the general symptoms are usually less severe.

Diagnosis.—Lymphangitis must be distinguished from phlebitis. The general symptoms are alike, but in phlebitis the thrombosed vein when palpable is felt as a larger and deeper-seated cord, less painful on pressure. The skin is but slightly reddened or not at all, the regional lymph glands are rarely involved, while the pain is less and the fever not so high.

Prognosis.—The simple form usually recovers in a short time, the length of the course of the affection depending upon the general condition of the patient. Recovery is delayed in cachectic and enfeebled patients. In the purulent form the prognosis is graver, since the danger of pyæmia or septicæmia is great. After extensive suppuration of a lymphatic vessel or group of vessels a condition of chronic œdema of the region concerned may develop, and perfect recovery from this condition is not likely to occur.

Treatment.—An evident cause of infection should be removed according to proper surgical methods. Extreme tension may be relieved by incision. In the involvement of the lymphatics of an extremity the limb should be elevated and complete rest enjoined. In the case of small, localized areas of lymphangitis hot or cold antiseptic dressings may be applied. Particularly in the case of the "sore nose" or "sore lip," coming so frequently under the physician's notice, do hot moist antiseptic compresses lessen the discomfort and apparently shorten the process. Early treatment may prevent the formation of herpes. In many of these cases, it should be remembered, the localized lymphangitis of the respiratory openings is often a forerunner to a severe catarrhal inflammation of the respiratory tract, rhinitis, tonsillitis, bronchitis, or pneumonia. Such cases should, therefore, be treated with a view of preventing the further extension or generalization of the infection. Patients who have the symptom of localized painful swellings of the lips or nose, either with or without herpes, should be put to bed and supporting and eliminating treatment carried out. The local application of astringent solutions rarely does any

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good, although there is a widespread belief in their efficacy in aborting such inflammations when they are used in the early stages.

Simple lymphangitis may be successfully treated by local and general methods without resorting to surgical measures, but all cases of purulent lymphangitis should be regarded as surgical affections as soon as their nature is discovered. The general treatment of such cases consists also of supporting and eliminating measures. A liberal soft diet should be advised, the bowels should be kept open, and tonics and stimulants administered according to indications. Likewise, the degree of pain and prostration must govern the use of sedatives, hypnotics, or analgesics. Massage and various measures such as bandages, casts, hydro- and electrotherapy may be necessary after the process has subsided in order to combat the stiffness and œdema often persisting.

Chronic Lymphangitis.—Chronic inflammation of the lymphatics may be caused by the presence of parasites (filariæ) within the lymph vessels, chronic infections (gonorrhœa, syphilis, tuberculosis, bubonic plague, etc.), absorption of products from neighboring ulcers or abscesses, extension of malignant tumors into the lymphatics, etc. In the lymph capillaries the endothelial cells become swollen or hypertrophic, so that in microscopic sections the vessels may resemble gland ducts or may be mistaken for strands or cords of carcinoma cells. In the large lymphatics there may occur further a proliferation and induration of the connective tissue of the vessel wall and of the surrounding tissues. This may in time lead to a complete obliteration of the vessel. Pathologically there may therefore be distinguished the forms known as *endolymphangitis proliferans* or *productiva* and *lymphangitis productiva* and *fibrosa obliterans*. As the result of the obliteration of the lymph vessels a chronic œdema and elephantiasis of the region tributary to the affected vessels may develop. Productive and obliterative lymphangitis are very common in inflamed serous membranes and in the lungs. In the latter the obliteration of the lymphatics as the result of chronic inflammation plays a very important part in the production of anthracosis and in the development of later affections of the lungs. An obliterative lymphangitis is very common in the lymph vessels leading from a part affected by a malignant tumor, even when no extension of the growth into the lymphatics has occurred.

Only when the large lymph trunks or the superficial lymphatics are the seat of chronic inflammation are clinical symptoms evident. Chronic œdema, elephantiasis, lymphorrhagia, lymph fistula, chyluria, etc., are the most important clinical features. In the case of superficial lymphatics the thickened and indurated vessels may be felt as firm cord-like structures. The involvement of a local plexus of lymphatics may give rise to a tumor-like formation (lymphangioma circumscriptum, etc.).

Treatment.—The treatment of chronic lymphangitis is concerned chiefly with the removal of the etiological factor and the improvement of the lymph stasis, œdema, or elephantiasis that may have resulted. The latter is partly surgical and in part medical. In the latter case the indications are similar to those for the treatment of acute lymphangitis.

Tuberculosis.—Secondary tuberculosis of the lymph vessels is very common, particularly in those of the mesentery and intestine. In the superficial vessels of the extremities it is more rare, and occurs usually in association with lupus or tuberculous ulcers of the hands or feet. Miliary tubercles

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may be found in the walls of the lymph vessels leading from the affected part, or the vessel may be diffusely enlarged, appearing as a firm, cord-like structure. Abscesses may develop along its course. In the leg a string of nodules or abscesses may be found along the saphenous vein. Tuberculous lymphangitis occurs also in the lymphatic vessels running to the axillary nodes in association with primary tuberculosis of the mamma. As the result of a retrograde metastasis within the superficial lymphatics of the thorax, tuberculous abscesses may develop in cases of mammary tuberculosis at any point in the skin of the affected side of the thorax. The axillary glands are always involved in such cases.

In the lymphatics of the mesentery and intestine a more or less marked tuberculous lymphangitis and perilymphangitis may be observed in cases of intestinal tuberculosis. The course of the lymph vessels may be shown by a tortuous string of grayish-white nodules corresponding to tubercles within or near the lymph vessels. The blocking of the vessel lumen by the tubercles or by caseous detritus may lead to a lymph stasis. In the generalization of the infection the involvement of the lymphatic vessels plays a most important role.

Treatment.—The local treatment of tuberculous lymphangitis is chiefly surgical. The medical treatment is embraced in that accorded tuberculosis in general.

Syphilis.—The lymph vessels in the neighborhood of the primary sore are always the seat of a more or less marked syphilitic inflammation. In the neighborhood of secondary lesions the lymphatics are likewise involved. In the late stages a local or generalized thickening of the walls of the lymphatics may occur, and rarely gummata may be found developing within the walls of the large lymph trunks.

Lymphangitis also occurs rarely in *leprosy, glanders, plague*, etc., as a part of the specific infection, and appears clinically as a complication of these conditions. The treatment of all these forms of specific lymphangitis is embraced in the general treatment of these diseases.

Lymphangiectasia.—Dilatation of the smaller peripheral lymphatics results from an obstruction or obliteration of the larger trunks when the collateral circulation is inadequate. Such an obliteration may be the result of a proliferative endolymphangitis, tuberculosis, carcinomatous infiltration of the wall of the lymph vessel, syphilis, etc., or an obstruction to the lymph flow may be due to the presence of parasites, pressure upon the lymph vessels, contraction of the surrounding tissue (perilymphangitis), removal or disease of the regional lymph glands, etc. In the superficial lymphatics ectasia is in the great majority of cases, if not in all, associated with or is the result of a chronic inflammation. In the mesentery dilatation of the chyle vessels is often the result of a tuberculous lymphangitis.

The smaller branches of the obstructed trunks usually show the dilatation in the most marked degree. In the mesentery the dilatation of the smaller lymphatics manifests itself in the form of localized cysts (chyle cysts) or as a more extensive varicosity of a lymph plexus. When the dilatation is marked, lymphorrhagia may occur, giving rise to *chylous ascites*. A similar condition in the lymphatics of the thorax may lead to *chylothorax*. In the skin the dilatation of the lymphatics leads to a chronic œdema of the affected area, and with this there may be associated a connective-tissue hyperplasia, giving rise to the condition known clinically as *pachydermia*

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or *elephantiasis lymphangiectatica* when involving an extensive area, or, when localized, appearing as a variety of *lymphangioma*.

Elephantiasis Lymphangiectatica or Lymphangitica.—Synonyms: Pachydermia; elephantiasis Arabum; morbus herculeus; spargosis; tropical big leg; pucnemia tropica; phlegmasia Malabarica; mal de Cayenne; Barbadoes leg; sarcoma mucosum; hypersarcosis.

Special interest attaches to elephantiasis through the fact that this condition is frequently mentioned by the medical writers of antiquity. There can be but little doubt, however, that the term elephantiasis Arabum was formerly used in a very loose way to designate a great variety of conditions in which there was a local enlargement of the tissues, particularly those of the skin. At the present time the use of the term has been narrowed to those affections of the skin and subcutaneous tissues characterized by a hyperplasia of the connective tissue, either diffuse, or localized to the bloodvessels, lymph vessels, or nerves. A lipomatous form also occurs. The most common variety, however, is that one involving the lymphatics, its general character being a chronic and progressive enlargement of a certain portion of the body due to a hyperplasia of the connective tissue of the skin and subcutaneous tissues, hyperplasia of the lymph vessels, chronic œdema and rarely a cellular proliferation or infiltration. It occurs as an endemic disease in the tropics and sub-tropics, and as a sporadic affection throughout the remaining regions of the globe.

Etiology.—The etiology of the lymphangitic form of elephantiasis is varied. It may appear as a *spontaneous congenital* or *inherited* condition, or it may be *acquired*. In the acquired forms of elephantiasis lymph stasis due to various etiological factors plays the most important role. The majority of the tropical cases are due to the presence in the lymph vessels of the *Filaria sanguinis*, a condition of lymph stasis, chronic lymphangitis and chronic inflammation of the skin being produced by the presence of the parasite. The sporadic acquired cases are often the result of chronic erysipelatous or eczematous inflammations of the skin involving the lymphatic vessels. Any cause of chronic or recurring lymphangitis may lead to an elephantiasis of the affected region. Lupus, syphilis, varicose ulcers (Fig. 55), frost-bite, traumatism, etc., are among the numerous etiological factors. The removal or destruction of the regional lymph glands may be followed by elephantiasis of the part tributary to the glands. For example, after the removal of the axillary glands for secondary carcinoma or tuberculosis, a chronic œdema and elephantiasis of the arm may follow. The condition may be temporary or permanent. Likewise, removal or destruction of the inguinal glands may be followed by elephantiasis of the genitals and thighs. Chronic œdema due to thrombophlebitis may also form the basis for the development of an elephantoid condition. Congenital acquired cases have been observed, apparently due to an intra-uterine infection. The *spontaneous* forms of elephantiasis are those in which the anlage of the condition is apparently an intrinsic one, the disease developing slowly without any exciting cause or signs of inflammation. Such cases, even when developing in adult life, are regarded as congenital or inherited. In some instances a definite family history of inheritance of the affection is present. The disease occurs at all ages, but naturally is most frequent in adults. Males are more frequently affected in the tropics; in temperate regions the majority of the sporadic cases occur in women.

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Pathology.—The legs and external genitals are most frequently involved, although the affection may occur in any superficial part of the body. Next to the lower extremities and genitals, the hand, arm, face, ears, and mammæ are involved, in frequency according to the order given. The affected parts may be hard and indurated (*elephantiasis dura*), or soft and pitting on pressure (*elephantiasis mollis*). The epidermis may be smooth (*elephantiasis glabra*), papillary or warty (*e. papillaris* or *verrucosa*), or nodular (*e. tuberosa*). The horny layer may be greatly thickened, presenting

FIG. 55

Acquired elephantiasis due to varicose ulcers.

the appearances of ichthyosis. The skin may be pale, shining, and more translucent than normal, or it may be more or less pigmented (*e. fusca* or *nigra*). The natural folds of skin are greatly exaggerated and the surfaces between them are usually moist and have an offensive odor. Ulcers, abscesses, chronic eczema, secondary atrophic and degenerative changes complicate the picture. The affected parts increase greatly in bulk and weight; the scrotum may attain a weight of 100 pounds or more, while the extremities may exceed in circumference the trunk. From ulcerated surfaces a large amount of lymph may escape (*lymphorrhagia*). The fluid

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is often milky white. Varicose lymph vessels are sometimes seen on the surface, which may rupture and a *lymph fistula* result. This is more frequent in the lymphangiectatic form of the disease, and particularly when the genitals are involved.

The microscopic examination of tissue showing the lymphangitic form of elephantiasis reveals a hyperplasia of connective tissue and lymph vessels. The new fibrous tissue may be very poor in cells, or it may resemble a cellular granulation tissue. The lymph capillaries are dilated, and there is usually marked œdema. A definite new formation of lymph vessels appears to take place and the walls of the existing lymphatics become thickened. Numerous plasma cells may be scattered through the tissue, and areas of lymphoid infiltration may be present. All the structures of the skin may be involved in the connective-tissue infiltration and may be gradually destroyed by pressure. The intermuscular connective tissue may also become greatly increased and the muscles gradually destroyed. Osteomata may develop in the new-formed connective tissue, and the bones may become irregularly thickened as the result of a periostitis ossificans. Eventually, atrophy or necrosis of the bones may result. The pathological picture in all cases of lymphangitic elephantiasis is practically the same, no matter how varied the etiology. The disease, therefore, presents a unity in its pathological anatomy.

Symptoms.—The early symptoms of elephantiasis vary greatly according to the cause; but the general symptomatology of the condition when it has developed is similar in all cases, no matter what the cause. In the spontaneous forms there may be no symptoms except the resulting deformity, and in advanced cases the secondary symptoms arising from pressure, atrophy, ulceration, etc. The endemic or parasitic form (filarial elephantiasis) has a definite clinical picture of infection. The sporadic cases due to erysipelatous or eczematous inflammations affecting the lymph vessels of the skin have also a definite symptomatology according to the nature of the cutaneous condition. Chills, fever, swelling of the regional lymph glands, etc., may precede or accompany the development of the condition. When due to a chronic lymph stasis unattended by inflammatory changes, the condition develops gradually out of a chronic œdema without special symptoms.

The local discomfort may be great. In all forms of elephantiasis severe neuralgic pains may attend the enlargement of the part, but in the later stages a certain degree of anæsthesia results from the destruction of the nerve trunks and endings. The deformity gives great annoyance and the effect upon the general character and disposition may be very marked. Insanity, suicide, melancholia, etc., may result from the nervous worry. The great bulk and weight of the affected part may make the patient helpless or greatly interfere with his movements. Dislocation of the affected extremity is not infrequent, and in the later stages fractures of the bone may occur. Elephantiasis of the genitals usually leads to an interference with or a loss of the sexual function. Coitus becomes an impossibility and the affected portions become more or less anæsthetic. The patient's unhappy state is increased by the occurrence of secondary ulcers, fissures, abscesses, etc.

The condition of elephantiasis develops usually very slowly, but in some cases there is a very rapid growth, large tumors being formed in a short time. This is especially true of the sporadic cases of elephantiasis of the

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vulva. Ordinarily it takes years for tumors the size of a hen's egg to form, but in some cases the tumors quickly reach a great size. Such forms are often mistaken for sarcoma.

Prognosis.—In so far as the elephantoid condition itself is concerned, the prognosis is not good except in those cases in which surgical treatment is possible. A certain number of cases are cured by operation. The condition itself does not shorten the patient's life, with the exception of those cases complicated by secondary infections. The chances for an improvement in the cases due to simple lymph stasis are good under appropriate treatment.

Treatment.—For the treatment of the endemic (filarial) form of elephantiasis, see Vol. I, p. 619. The sporadic cases met in temperate climates are best treated by the improvement or removal of the etiological factors. Varicose ulcers should be promptly healed; the venous outflow should be aided by position, bandages, etc. All causes of inflammation should be combated. In the case of the chronic erysipelatous or eczematous conditions of the skin, or in recurring local lymphangitis vaccines may be prepared and used. The hope is aroused that some of these cases may be successfully treated by this method. The chronic œdema of the arm following the removal of the axillary glands may be prevented from developing into elephantiasis by the proper use of bandages, etc. Such cases often recover spontaneously after a number of months. If, by proper treatment, during this time the condition is reduced to a minimum and secondary infections prevented, the elephantoid hyperplasia may be inhibited so that with the restoration of the lymphatic circulation in the axilla the extremity resumes either wholly or in part its normal condition.

The ultimate treatment of advanced cases becomes surgical. Ligation of the arteries has resulted in cures. Resection or stretching of the sciatic nerve, removal or amputation of the affected portions of the skin, amputation of the extremity, etc., are among the surgical measures advocated. The general treatment in these cases is along supporting and antiseptic lines.

Neoplasms.—Tumors arising from or composed of lymph vessels are of very frequent occurrence. They may be divided into two classes, the *lymphangiomas* and the *endotheliomas*. The first-named neoplasms are wholly benign in character, while those belonging to the second class are in part benign and in part malignant.

Lymphangioma.—The neoplasms classed as lymphangiomas consist for the chief part of spaces lined with endothelium and containing lymph. The walls of these lymph spaces may be thick or very thin; in either case the lymph spaces themselves may be small or ectatic. These growths occur chiefly in the skin and subcutaneous tissue, but may be found also in internal organs. They may be diffuse or circumscribed, flat or nodular, and in the skin are frequently attended by a marked pigmentation of the epidermis and by an overgrowth of hair. The majority of the pigmented moles and nævi, fleshy warts, etc., belong to this class. In many cases it is impossible to say whether the condition represents an actual new formation of lymph vessels or simply a dilatation of preëxisting ones with a secondary hyperplasia of the vessel walls. Lymph stasis plays a very important role in the development of some of these lymphangiomatous conditions. Those forms in which an actual proliferation and new formation of lymph vessels occurs may be classed with the true neoplasms. Three forms of the latter may be distinguished: *lymphangioma simplex*, *l. cavernosum* and *l. cysticum*.

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The most common clinical forms of these neoplasms are certain varieties of pigmented spots and patches, nævi, warts, moles, etc., of the skin and tongue, the diffuse cavernous lymphangiomata of the tongue and lips known as macroglossia and macrocheilia, the cystic tumors of the neck (*hygroma cysticum colli congenitum*) and the cystic lymphangiomatous tumors of the arm, trunk, mesentery, and thighs. These tumors are for the greater part congenital, and may be so large at birth as to hinder delivery.

Endotheliomas.—Neoplasms arising through the proliferation of endothelium either of the bloodvessels or lymphatic vessels may be classed as endotheliomas. Those arising from the endothelium of the lymphatics (*lymphangio-endothelioma* or *endothelioma lymphangiomatosum*) will alone be considered here. These neoplasms belong histogenetically to the connective-tissue tumors; the benign forms may be classed with the typical varieties of this group, while the malignant forms are analogous to the sarcomata. In general the malignant endotheliomas are relatively less malignant than sarcomas. The very cellular endotheliomas are not necessarily malignant, since many of this nature are found in the parotid gland running clinically a perfectly benign course. On the other hand, the endotheliomas of the inner meninges are usually very malignant. Many writers deny the existence of a distinct class of endotheliomas, preferring to group these neoplasms either with the lymphangiomas, sarcomas, or even the carcinomas. The microscopic diagnosis is often very difficult, since it is often impossible in the case of a fully developed endothelioma to determine whether its cells have arisen through the proliferation of endothelium or have simply replaced the latter in the lymphatics. Nevertheless, in many instances such a histogenesis can be determined for the tumor cells.

The most common clinical forms of the endothelioma are the fleshy wart (lymphangioma hypertrophicum), the endotheliomas arising from the lymph spaces of the peritoneum, pleura, dura mater and inner meninges, the endothelial tumors of the salivary glands, mamma, testis, and ovaries, and more rarely those occurring in the face, mouth, uterus, etc. In the case of the endothelial tumors of the serous membranes the growth of the endothelium in the lymph capillaries gives rise to a microscopic picture suggesting the structure of an epithelial tumor, adenoma, or carcinoma; and these neoplasms are often diagnosed as the latter. Many of the tumor forms known as psammoma and cylindroma belong to the endotheliomas. The endothelial tumors of the salivary glands show a special inclination to mucoid degeneration.

Prognosis.—In the case of the great majority of the lymphangiomas of the skin the neoplasm runs a benign course, and aside from cosmetic reasons occasions no trouble. Many of them are easily removed and do not return. In other forms, as, for example, the *lymphangioma circumscriptum* of the skin, recurrence usually takes place. Malignant change sometimes occurs, as, for instance, the not infrequent development of melanotic sarcoma in pigmented lymphangiomas of the skin. In general the endotheliomas of the salivary glands, dura mater, and skin run a relatively benign course, particularly the first named. Those of the inner meninges and serous membranes have about the same degree of malignancy as sarcomas. The endotheliomas of the mamma, ovaries, and uterus are much less malignant than sarcoma or carcinoma of these organs, metastases being less frequent and the course of the affection longer.

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Treatment.—The treatment of primary tumors of the lymph vessels is purely surgical. Electrolysis, Röntgen irradiation, excision, etc., are the methods advocated.

Secondary Neoplasms.—The smaller lymphatics form the chief highway by which the local spread of carcinoma takes place. The carcinoma cells break directly into the lymph capillaries, dilate them, and grow in them as solid plugs or cords of cells. The wall of the lymph vessel may become thickened, but may remain uninvolved by the cancer cells for some time. Such carcinomatous outgrowths in the lymphatics may be seen at some distance from the primary tumor, and are often regarded as metastases, whereas serial sections show their direct continuity with the primary. This is particularly true of the lymphatic vessels running from the mamma to the axillary glands; in cases of mammary cancer such vessels often appear as solid cords of tumor cells. The lymphatic capillary plexuses over an extensive area may be completely infiltrated by carcinoma in some cases, as in secondary carcinoma of the pleura or peritoneum, where the lymphatics of the entire surface may appear thickened and beaded like a rosary, and filled with carcinoma plugs.

Nevertheless, certain forms of sarcoma extend by preference through the lymphatics, as, for example, *lymphosarcoma*, *chondrosarcoma*, and certain sarcomas of the bones. All of the forms of sarcoma arising from *free* mesoblastic cells (choroma, aleukæmic and leukæmic lymphocytoma, myeloid leukæmia, etc.) extend through the lymphatics as well as through the bloodvessels. The spread of a malignant *endothelioma* is likewise largely accomplished by means of the lymph vessels.

Treatment.—The treatment of secondary malignant tumors in the lymphatics is purely surgical. The important point, however, in regard to such treatment is the necessity of removing a large area of apparently normal tissues about the primary growth in order to get out the extensions into the neighboring lymphatics.

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PART II.

DISEASES OF THE BLOOD.

CHAPTER XIV.

THE GENERAL PATHOLOGY OF THE BLOOD-FORMING ORGANS.

By RICHARD C. CABOT, M.D.

Preliminary Considerations.—Before discussing the diseases of the blood it is well to give some consideration to the data on which our knowledge of these diseases is founded, and some definition of the terms employed. The data referred to are:

1. Accumulated knowledge regarding blood-formation, in embryonic and postnatal life.
2. The studies of the blood-making tissues (marrow, spleen, and lymph glands), made possible by recent improvements in hæmatological technique.
3. The data of clinical blood examination, and the methods by which they are obtained.

Without attempting to summarize the whole subject of blood formation, a few of the main facts may be indicated. The blood-making system, marrow, spleen, and lymph glands, attains only gradually the differentiation seen in adult life. In fœtal life, the distinction between leukocyte-producing and erythrocyte-producing tissues is much less sharp, and throughout the whole system both red and white cells are produced. Further, in the embryo the liver shares with the organs just mentioned the function of blood production. In the adult, however, specialization has become an accomplished fact. Red cells are produced exclusively, or almost exclusively, in the bone-marrow. Leukocytes are produced in the marrow, spleen, and lymph glands. A few of the lymph glands, especially the hæmolymph glands, may continue their embryonic function of producing red cells, and under the stimulus of various diseases, return to their embryonic function.

The source of the different varieties of leukocytes which we find in the circulating blood in adult life is now approximately agreed upon, at any rate as regards the great majority of the cells. All varieties of granular leukocytes (neutrophilic myelocytes, polynuclear neutrophiles, eosinophiles, and mast cells) are formed in the bone-marrow. Lymphocytes are formed

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in the lymph glands and lymphatic tissue generally. The points still in doubt are: (*a*) Does the marrow in health furnish any considerable number of lymphocytes to the circulating blood? (*b*) What is the source of those mysterious cells closely resembling, but not identical with, large lymphocytes, and usually referred to as "large mononuclear" cells? These questions will be discussed later.

In the formation of red cells in adult life, which occurs wholly or almost wholly in the bone-marrow, the earliest stages are represented by nucleated cells somewhat larger than those seen in the circulating blood, but not so large as those seen in the fœtal marrow and in the marrow of the lower vertebrates. Later in the course of this development, but before it leaves the marrow, the red cell normally loses its nucleus. Whenever, therefore, nucleated red cells are found in the circulating blood, they are regarded as immature, unfinished cells, and their presence is taken to indicate an unusual activity of the red-cell-forming tissues—probably an unusual need on the part of the body for new red cells.

In the formation of granular leukocytes in the adult marrow, we find, first, mononuclear cells (neutrophilic, eosinophilic, or basophilic), which later in the course of their development, and usually before they enter the circulating blood, have developed a polymorphous nucleus. Mononuclear neutrophiles or myelocytes are thus the ancestors of the polynuclear neutrophilic cells of the circulating blood. Mononuclear eosinophiles, or eosinophilic myelocytes, are the ancestors of the polynuclear eosinophiles of the circulating blood. The mast-cell nucleus, as seen in the circulating blood, is so vague and difficult to make out that it is impossible to say just what change it has undergone since it left the marrow.

Whenever there is a call for large numbers of fresh *leukocytes* in the circulating blood, a call such as occurs in many types of infectious disease and in the leukæmias, the marrow sends out, first, the accumulated stores of finished polynuclear cells, which are resting in the sinuses of the marrow. When these are exhausted, if new formation goes on rapidly and is not inhibited by the virulence of the attacking disease, the earlier stages of the polynuclear, granular cells begin to appear in the peripheral circulation. The process is very closely parallel to that which occurs when there is a call for large numbers of new-formed *red cells*. First, the accumulated stock on hand is sent out; then the half-formed, immature cells are discharged into the blood stream. Finally, if the demand for new cells is long continued, the process of blood formation may revert to an earlier (fœtal) type, and we begin to see in the circulating blood cells which are strangers not only to the blood, but also to the normal adult marrow, and only to be found in the fœtal marrow or in lower animals. On the part of the red-cell series, these embryonic cells are represented by the megaloblasts. Just what cells represent the earliest stages of leukocyte formation in the marrow is a point more or less disputed, but the weight of authority inclines to the belief that many of the cells seen in acute lymphoid leukæmia represent this ancestral, undifferentiated type.

Most observers are now coming to agree that as we trace back each of the stocks just referred to, the red cell series on the one hand and the leukocyte series on the other, we approach a common ancestor, which is in all probability a round mononuclear, non-granular cell, with basophilic protoplasm. In all the more extreme disturbances of blood formation, whether

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they affect especially the red cells, as in the various types of anæmia, or the white cells, as in the leukæmias, we begin to find in the circulating blood, and especially in the marrow, considerable numbers of cells which approach this ancestral type, and many which are difficult to assign to either the red cell or the white-cell series. No attempt will be made to go into the controversies or discuss the terminology of these ancestral cells. The problems concerning them have been exhaustively discussed by Pappenheim in recent numbers of the *Folia Hæmatologica*. Suffice it here to say that it is now generally agreed that in the leukæmias the marrow, spleen, and lymph glands all begin to turn out cells much less differentiated, much nearer to the ancestral type than are discharged from those organs in health.

The formation of lymphocytes in the lymph glands in the thymus, tonsils, and in the lymphatic tissue scattered diffusely about the alimentary canal and elsewhere, begins in groups called "germ centres," where cell division is especially active. From these the new-formed cells are extruded peripherally, and group themselves radially. From the periphery of these groups they reach the sinuses and are carried into the lymphatic stream and into the blood current. In the germ centres we have cells closely resembling the large lymphocytes of the peripheral blood. Toward the periphery of these centres we find cells of smaller size and with deeper-stained nuclei, cells, that is, which correspond accurately to the small lymphocytes of the circulating blood.

In leukæmia of the myeloid type and in some conditions of infection or auto-intoxication (scarlet fever, cancer), these lymph glands may be transformed into a tissue closely resembling the marrow; all the varieties of granular leukocytes then begin to be formed, so that it may be difficult to distinguish a section of such a gland from a section of the marrow. On the other hand, in generalized tuberculosis or carcinoma of the lymph glands, the number of circulating lymphocytes may be greatly and permanently diminished (300 to 500 per cmm.—Naegeli).

All that has been said of the lymph glands holds good of the Malpighian bodies of the spleen. Normally the seat of lymphocyte production, they may be transformed in myeloid leukæmia into tissue almost indistinguishable from bone-marrow; while in lymphoid leukæmia (ancestral?) cells not found normally either in the marrow or in the lymph glands, cells resembling but not identical with the lymphocytes of the germ centres, begin to be formed and turned into the blood stream throughout the lymphatic system.

THE MAIN DATA OF HÆMATOLOGY.

The most important facts upon which our present knowledge of diseases of the blood is built up are the following:

1. The number of red cells per cubic millimeter, as counted in the peripheral circulation.
2. The number of white cells and blood platelets, as counted under similar conditions.
3. The percentage of hæmoglobin in the circulating blood.
4. The appearances of stained film specimens of the peripheral blood.
5. The appearances of smears and sections of the blood-making tissues, marrow, spleen, and glands.

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6. The gross changes in the size of those portions of the blood-making system accessible to our examination, namely, the spleen and external lymph glands.

7. The clinical manifestations relating to the other organs and tissues of the body.

The technical details and methods by which these data are obtained would be out of place in an article of this kind. For them the reader is referred to the text-books of clinical blood examination. Here it will suffice to indicate in outline the results obtained.

The Enumeration of Blood Cells.—Briefly stated, our method of obtaining an estimate of the richness of the peripheral blood in *red corpuscles* is: (*a*) To obtain a measured quantity of capillary blood by puncture; (*b*) to dilute this with a harmless solution, which will enable us to separate and so count the crowded red cells; (*c*) to enclose a measured quantity of the diluted blood in a chamber of measured size, on the floor of which the corpuscles are then allowed to settle; (*d*) to count (with the aid of a moderately high power of the microscope) the number of cells in a measured area of the floor of the "counting chamber." The floor of this counting chamber is ruled off in squares of known size, and since the cells resting on it have settled out of a known bulk of fluid, which in turn corresponds to a known bulk of blood, we may compute from the number of cells thus counted what was the number in a cubic millimeter of the sample of blood originally drawn.

It is well to indicate some of the limitations of this method and some of the possible sources of error. The actual enumeration as described gives a fairly accurate idea of the number of cells in the unit of peripheral blood selected for study; but when we come to draw conclusions from the figures thus obtained, we must remember: (*a*) That these figures tell us nothing at all about the total amount of blood in the body. They represent simply the corpuscular richness of a small, although presumably representative, specimen of the whole blood. Thus it may be that when we find in a case of advanced phthisis a cubic millimeter of blood containing approximately the normal number of corpuscles—5,000,000 or thereabouts—the patient is nevertheless anæmic, in the sense that his tissues are bloodless, and his bloodvessels more empty than the normal. In other words, all estimates of the richness of the patient's blood by means of a count of red corpuscles must be interpreted as qualitative rather than quantitative statements. They show us whether the sample drop of blood which we draw is of the proper quality; but they do not show at all how much blood there is in the body.

(*b*) In certain conditions, especially in those involving cyanosis, peripheral congestion, or dropsical states, the drop which we draw may very imperfectly represent the condition of the rest of the blood mass. In cyanotic and congested conditions, red cells accumulate at the periphery, and the number which we find in a cubic millimeter of blood drawn by ordinary puncture is far in excess of the average number which would be found in the blood of the larger vessels, or within the internal organs.

(*c*) A drop of blood drawn immediately after the patient has suffered a large hemorrhage shows approximately normal conditions. Within a few days, or sometimes within twelve hours, a second count would reveal a very much smaller number of red cells per cubic millimeter. This is simply

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because the normal amount of fluid has by that time been taken up by the bloodvessels from the other tissues, and ultimately from the fluids ingested. By the fluid so taken up the relatively empty vessels are now refilled and the blood diluted. The second estimate made after this dilution has occurred makes us aware of the loss suffered by the patient; while if we had followed the estimate made immediately after the hemorrhage, we might have supposed that no loss had occurred. It should be remembered, however, that regeneration begins so promptly that even before the blood has regained its normal bulk of fluid by absorption from the tissues, the number of red cells has begun to approach normal, owing to the rapid regeneration and extrusion of new red cells in the marrow.

The enumeration of *white corpuscles* is accomplished in essentially the same way by which the red cells are counted. By making use of 0.5 per cent. of acetic acid as a diluting fluid, we render the red cells invisible, and can count the white cells without difficulty. The many factors and influences which control the number of white cells in the peripheral blood in health and disease, and the distribution of the various types of leukocytes within the total leukocyte count, will be discussed in the section on Leukocytosis and Leukopænia.

Hæmoglobin Estimation.—Since hæmoglobin is, so far as we know, the important functional element in the red cells, the amount in a unit of blood would be, could we accurately measure it, equivalent to the amount of functioning red-corpuscle substance. There seems no good reason to doubt that the bulk or weight of hæmoglobin in a given unit of blood can be measured with reasonable accuracy by an estimate of the intensity of the color sensation produced by that quantity upon the eye. The various clinical methods of estimating hæmoglobin are accordingly based upon this presupposition, and the color of the blood, either diluted or undiluted, is accordingly compared with a standard scale of colors arranged to correspond with the color of normal blood, with the color of blood lacking 10 per cent., 20 per cent., 30 per cent., and so on of the normal. Of the usefulness and reliability of the different methods of testing hæmoglobin no judgment is attempted here.

Color Index.—What is known as the *color index* in hæmatological terminology refers to a ratio between (*a*) the number of corpuscles stated in percentages and (*b*) the percentage of hæmoglobin. When the red corpuscles are 100 per cent. of their normal number, and the hæmoglobin is 100 per cent. of its normal color, we say that the color index is 1; but if the amount of coloring matter per cell becomes reduced one-half, while the number of cells remains normal, so that we have 100 per cent. of corpuscles with only 50 per cent. of hæmoglobin, we say that the color index is 0.5. If, on the other hand, as in pernicious anæmia and in some other grave types of anæmia, the red corpuscles are reduced to (say) 20 per cent. of their number, while the hæmoglobin reads 30 or 40 per cent., we say that the color index is high—that is, above 1. Thus, 40 per cent. of hæmoglobin with 20 per cent. of corpuscles means a color index of 2. Such a color index is generally assumed to be due to an increase in the amount of hæmoglobin contained in each corpuscle, and there seems no reason for doubting that this assumption is correct, since in all cases in which the color index has been found high an increase in the size of the red cells has been apparent in film preparations.

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With the application by Ehrlich of aniline dyes to the staining of blood films, our first clear insight into the details of blood pathology began. With the introduction of a new staining method within the past nine years has come both increase of knowledge and a very considerable confusion through the modification and partial annihilation of a good many of our previously acquired ideas. The advent of the "Romanowsky" method of staining, with its host of variously named modifications,[1] has effected a renewal of activity and interest, but also an obscuring of old landmarks, comparable to what has been produced by the "higher criticism" in biblical literature.

Staining Affinities of the Red Cell in Health and Disease.—The new knowledge which began with Ehrlich rested upon the discovery of certain affinities in the protoplasm of the red and of the white cells for one or another coloring matter of the aniline-dye series. Thus the protoplasm of red cells in the peripheral vessels of healthy adults takes up and is stained by coloring matters belonging to what is called "the acid series," such, for example, as orange-G, acid fuchsin, and eosin. For these stains the red-cell protoplasm has an affinity greater than its affinity for any of the so-called "basic stains," of which methylene blue is the type. When exposed to a staining fluid containing both an acid and a basic dye, normal red cells take up only the acid stain; although it is true that they can be colored to some extent by a basic dye, if no acid-coloring matter is present at the same time.

Under pathological conditions, however, we find in the peripheral circulation red cells which take up a varying quantity of a basic dye when exposed to a coloring mixture containing both acid and basic principles. As a result, the red cell, instead of staining yellow, orange, pink, or red, as it does with pigments of the acid series, becomes more or less brownish, purple, or even blue, as it takes up more and more of the blue-staining basic dye. The conditions under which this double affinity takes the place of the normal single affinity in the red cell are not yet altogether understood, but certain points are clear. The red cells of the fœtal marrow and a considerable number of the immature cells of the adult marrow, including many of the erythroblasts, possess a considerable degree of affinity for basic coloring matters. This affinity may be either diffusely distributed over the whole cell, so that the cell stains an even purple or blue, or may be confined to a considerable number of minute points in the substance of the red cells, so that when such a cell is exposed to a mixture containing both an acid and a basic dye, a multitude of small blue or bluish-black points stand out sharply against the yellow or pinkish stained protoplasm around them. It has been much discussed whether these appearances are to be considered as evidence of youth or age in the corpuscle, some students vigorously maintaining that these abnormal staining reactions express a degenerative condition, while others, with whom the writer agrees, tend to believe that whenever these abnormal staining reactions are found, we are dealing with an immature or youthful cell.

In accordance with the conceptions above explained, we speak of the normal red cell in the circulating blood of adults as monochromatophilic; and of the diffusely brown, purple, or blue-stained erythrocyte as *polychromatophilic*. (See Plate IV, Fig. 1, M¹, M², M³.) When the basic staining

[1] Nocht's, Giemsa's, Ziemann's, Jenner's, Wright's, etc.

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occurs as a sprinkling of blue-black dots upon the corpuscle, it is often spoken of as "*stippling*" or basophilic granulation. (See Plate V, Fig. 1.)

Another evidence of the immaturity of the red cell, first clearly brought to light by Ehrlich's staining methods, is the presence of nuclei in the cells. These nuclei, like those of most of the body cells, are marked off and made visible in the cell by the fact that they have an intense affinity for basic (usually blue-staining) dyes, so that in the nucleated red cell we have, with the ordinary methods of staining, a dark-blue or greenish-blue nucleus outlined against a yellow or pinkish cell body.

Among the nucleated red cells of human blood two main types are distinguished: (*a*) normoblasts and (*b*) megaloblasts. The megaloblast, as its name implies, is the larger of the two. It is also the younger or more primordial cell, following the well-known histological law that the ancestors are larger than their descendants. The megaloblast is a cell relatively near to the primordial mother cell, from which spring all varieties of leukocytes and red cells. This primordial cell is considerably larger than the adult red cell, has a vesicular nucleus, and a non-granular, basic, or blue-staining protoplasm. The youngest recognizable megaloblast has also a basic protoplasm, although its tint is a peculiar, dusky, cloudy blue, different from any tint seen in leukocytes. (See Plate IV, Figs. 1 and 2, M¹.)

In the majority of megaloblasts the hæmoglobin can also be recognized as fine streaks or spots of yellowish or reddish color within the blue protoplasm. The nucleus of this very young red cell takes up a very considerable proportion of the cell body, and shows a well-marked loose-skeined structure. Later generations of megaloblasts have a protoplasm less and less basophilic, and more and more yellowish, are smaller than their ancestors, and contain a darker, smaller, more tightly-skeined ("pyknotic") nucleus. (See Plate IV, Fig. 1, M⁴, and Fig. 2, M².)

Finally, at the end of this series we reach the *normoblast*, which is of the size of a normal red cell, and possesses a protoplasm which is usually, although not invariably, without basophilia. In other words, most normoblasts stain yellow or pinkish with the ordinary staining methods; but in a certain, rather small, percentage, the protoplasm contains dark blue stained dots, or is diffusely grayish or purplish. (See Plate V, Fig. 2, N, and Plate VI, Fig. 1, N.)

The nucleus is much smaller than that of the megaloblast, and shows ordinarily very little trace of structure. It stains intensely blue or bluish-black, and is usually round. Sooner or later this nucleus disappears from the cell. As to the method of its disappearance considerable controversy has raged, one party maintaining that it is extruded from the cell, while the other party believes that it breaks up and disappears without being forced out (karyolysis). It is now generally believed that both these processes occur, although probably the latter is the more frequent.[1] At any rate, we frequently find nuclei of normoblasts separated into several pieces of various sizes, some of which stain very weakly, or are almost invisible. (See Plate IV, Fig. 2, T, T, T.) Now and then a cell is seen in which only a trace of nuclear matter can be made out. On the other hand, we certainly often find a

[1] Mitosis, or normal cell division, both in red and in white cells, is frequently seen in the blood-making tissues, and occasionally occurs in the peripheral blood, but has no special pathological significance there.

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nucleus outside its cell which gives every evidence of having come from a normoblast. Whether or not it has reached this position by the action of vital forces, or whether it is pushed out of the cell by the technique of spreading the blood upon coverslips, is a matter very difficult to decide.

Before leaving the subject of the pathology of the red cell, it may be well to mention here some morphological changes. The normal red cell is approximately round, and varies in diameter from 5 to 8 or 8½ μ. Whenever the conditions of the production of red cells in the marrow are disturbed, as in anæmias of a grave type, we begin to find in the circulating blood cells which vary much more than the normal in size and in shape—giant cells, 10 to 20 μ in diameter; dwarf cells, only 2 or 3 μ in diameter; and deformed cells, pear-shaped, horseshoe-shaped, oblong, etc. In some specimens of blood there is a very marked tendency toward an oval or sausage-shaped type, reminding us of the cells seen in the blood of many of the lower animals. To these morphological deviations are given the names: anisocytosis (variations in size) and poikilocytosis (deformities in shape). (See Plate IV, Fig. 1.)

Staining Affinities of the Leukocytes.—Before Ehrlich's time the only recognized distinctions between the different types of leukocytes were those based upon the size of the cell and upon the size and shape of the nucleus. We recognized mononuclear and polynuclear forms, but little attention was paid to the granules, which, even in the unstained blood, can be made out quite clearly, surrounding the nucleus and filling the protoplasm of the cell. In the unstained blood we can distinguish granules of a larger and of a smaller type, but that is all. By Ehrlich's staining methods it was shown that the fine granules filling the protoplasm of the polynuclear cells stain especially well in what is known as Ehrlich's tri-acid mixture, a differential acid stain, which contains an acid and a basic dye, and was for some time supposed to be neutral in reaction.

To the granules which show a special affinity for one of the colors of this supposedly neutral stain was given by Ehrlich the name *neutrophilic*, which has clung to them ever since. Nevertheless, it has been shown that these granules will stain, although less distinctly, with almost any dye of the acid series. The possession of neutrophilic granules is confined in the circulating blood of normal adults practically to the polynuclear cells (see Plate III, Fig. 1), but in the marrow we find that the mononuclear ancestors of these polynuclear cells also possess a neutrophilic granulation. Hence to these cells has been given the name *neutrophilic myelocytes*. (See Plate VI, Fig. 1, M, M, M.)

The granulations of the coarsely granular cells, recognizable in the unstained blood, were found by Ehrlich to have a special affinity for eosin and the other acid dyes, and hence were named by him *eosinophilic* cells. In blood films stained by Ehrlich's tri-acid mixture, these granulations take a copper-brown or tawny tint, contrasting with the violet or purple shade of the neutrophilic granules. With the Romanowsky stains these granules appear a brilliant crimson. (See Plate III, Fig. 2.)

A third variety of granules, noticed in a very small number of the leukocytes of circulating blood, takes up only basic dyes, and remains entirely unstained by Ehrlich's tri-acid mixture. With the Romanowsky stains these granules appear a dark-claret color or navy blue. (See Plate VI, Fig. 1 and Fig. 2, M A.)

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In the circulating blood of normal adults there occur in every hundred leukocytes from 60 to 70 per cent. of polynuclear cells with neutrophilic granulations ("neutrophiles"); from 0.5 to 3 or 4 per cent. of polynuclear cells with eosinophilic granules (eosinophiles); and from 0.1 to 0.5 per cent. of cells with basophilic granulations. The nucleus of this last type of cell is very difficult to make out, and its shape cannot be accurately seen in most specimens. To this cell is given the name *mast cell* by most writers, although by some they are spoken of as basophiles.

The *nuclei* of all the cells so far described take up the basic dyes, and appear of one or another shade of blue. In the polynuclear cells the nucleus is twisted, and takes on so great a variety of shapes that the term polymorphonuclear conveys a more accurate idea of the cell. In the eosinophile the nucleus is also polymorphous, but stains considerably less intensely than in the neutrophile, and has a much more loose-skeined structure. Indeed, the whole cell seems to be loosely constructed, for it is very prone to break apart in preparations which show no injuries in cells of other types.

Besides the three types of *granular* cells thus far described, we find in every hundred leukocytes of the normal circulating adult blood from 20 to 40 per cent. of *non-granular*, mononuclear cells, to most of which the term lymphocyte has been assigned by the majority of writers. Within this type at least two sub-varieties are to be distinguished: (*a*) The lymphocyte proper, a cell usually a little larger or a little smaller than a red cell, but sometimes almost twice this size. (See Plate VII, Fig. 1.) The nucleus takes up almost the whole of the cell, stains intensely with basic dyes, especially in the smaller forms, is almost always round or oval, and shows very little structure. The protoplasm may be either faintly acidophilic, or more often faintly basophilic. With Ehrlich's tri-acid mixture it is strictly non-granular. With the Romanowsky stain, a few bright pink granules are sometimes seen here and there around the nucleus ("azur" granules). (See Plate VII, Fig. 2, A.) Some writers deny the propriety of applying the term "granules" to these pink spots, but the point is too technical for discussion here. In the larger lymphocytes the nucleus stains less intensely, the protoplasm is a little more abundant, and the pink granules somewhat more numerous. Between these large lymphocytes and the forms next to be described every grade of transition occurs.

(*b*) To certain of the larger cells of the mononuclear, non-granular group, a great variety of names has been attached by different writers; thus, Ehrlich called them large mononuclear and transitional forms. Some of them certainly are identical with Türk's "stimulation cells," which of late he calls "plasma cells." (See Plate V, Fig. 1.) Others are referred to as non-granular myelocytes (Weil), lymphogonien (Benda), myeloblasts (Naegeli), and by many other titles. The nucleus is relatively smaller than in the large lymphocytes, often kidney-shaped or indented, often eccentrically placed, and shows a varying amount of structure. The protoplasm is relatively abundant, sometimes decidedly basophilic, and may contain a large number of azur granules. (See Plate VII, Fig. 2, L, L and A.) These cells make up from 1 to 10 per cent. of the leukocytes in normal blood, and are increased in a variety of pathological conditions.

There is no doubt that in this description several authors would recognize a confusion of their own favorite type with several others; but so long as the controversy concerning these cells continues to be as active as it has

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been for the past ten years, it does not seem wise to attempt further distinctions within the group just described.[1]

Origin of the Different Types of Leukocytes.—It is generally agreed, (*a*) that in healthy adults all the granular cells, including the polymorphonuclear neutrophiles, eosinophiles, and mast cells, with their mononuclear ancestral forms, come from the bone-marrow; (*b*) that the lymphocytes are supplied to the blood largely, if not wholly, by the lymphatic tissues of the body. Concerning the origin of the group of cells last described, the large mononuclear, non-granular variety, nothing certain can be said at the present time, but it is highly probable that a considerable proportion of them have their origin in the marrow. It is also probable that a small proportion of the lymphocytes of normal blood are formed in the marrow, but the number so formed is probably inconsiderable.

Blood Platelets.—Since the Romanowsky staining methods, which bring out the platelets sharply, have replaced so largely the methods used by Ehrlich, those which left the platelets invisible, interest in these structures has been renewed. Their origin, long disputed, seems now to be settled by the brilliant researches of J. H. Wright, who has presented very convincing evidence that they are pieces "pinched off" from the long processes of the marrow giant cells. They are increased in number in diseases which lead to a multiplication of giant cells (posthemorrhagic anæmia, leukæmia), and diminished in conditions like pernicious anæmia which are associated with a marrow poor in giant cells.

Thanks to the work of J. H. Pratt and others it is now possible to obtain a fairly accurate idea of the number of these structures in the peripheral blood, and it has been definitely established (*a*) that their number varies normally between 200,000 and 700,000 per cmm., (*b*) that they are considerably increased in pneumonia, posthemorrhagic anæmia and in myeloid leukæmia, and (*c*) that they are notably diminished in most cases of pernicious anæmia, in many fevers including typhoid and especially in purpura hemorrhagica.

In diameter they vary from 1 to 5 μ, but most of them are not far from 2 μ. They are usually oval in shape and tend to gather in large clusters like a bunch of grapes. Giant forms, as large as erythrocytes, occur in the severe anæmias. With the Romanowsky stains we see that they consist of a faintly blue-stained substratum, toward the centre of which a mass of magenta or dark-purple granules are clumped. No definite nucleus or structure can be made out.

For practical purposes one of the most important facts about the blood plates is the danger of mistaking them for malarial parasites, an error which occurs repeatedly. When a blood plate happens to settle upon a red corpuscle it becomes surrounded (for some reason not clear) by a white halo, marking it off from the stained red corpuscle substance around it. Under these conditions it bears a superficial resemblance to a young malarial parasite, from which, however, it may be readily distinguished by the absence of any definite blue-stained ring structure and of any red-staining nucleus.

Blood-making Organs.—1. **The Bone-marrow.**—In the normal adult the marrow is only in part a hæmopoietic tissue. It is composed to a

[1] Some of the other names for cells which are not morphologically or tinctorially distinguishable are Cornil's markcellen, Troje's markcellen, Müller's markcellen, Wolff's lymphoid cells, Pappenheim's splenocytes, and Pappenheim's piromyelocytes.

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considerable extent of fat, and serves presumably as one of the normal fat reservoirs of the body. The amount of this fat varies greatly in different bones, in different parts of the same bone, in different individuals, and in the same individual under varying conditions of health and disease. The fat is presented in the form of spots or islands, between which come cellular areas of erythroblastic or leukoblastic tissue. The erythroblastic areas have already been sufficiently described.

In the *leukoblastic areas* we find: (*a*) Neutrophilic myelocytes (50 to 60 per cent.), with a much smaller and variable number of their maturer forms, the polynuclear neutrophiles. (*b*) A small number of eosinophilic myelocytes and polynuclear eosinophiles. (*c*) A very small number (usually less than 1 per cent.) of mononuclear cells containing basophilic granules, and their adult forms, the mast cells. (*d*) A few cells closely resembling the neutrophilic myelocytes, but almost or wholly free from granules and more or less purely basophilic in their protoplasm. (*e*) A considerable number (15 to 30 per cent.) of cells *apparently*[1] identical with the lymphocytes of the circulating blood (no definite lymphoid follicles can be made out in the vast majority of normal cases).

In addition to these varieties, all of which can be frequently recognized in the circulating blood, we have two types of cells—both of which are occasionally found in the capillaries of the internal organs, but of whose presence in the circulating blood we have as yet no clear evidence. (*f*) The macrophage or giant cell, a cell of irregular shape and varying greatly in size (between 20 and 50 μ). Its nucleus is very irregular and convoluted or multiple, eccentrically placed, and stains intensely; its protoplasm is non-granular, faintly basophilic, and often occupied by a variety of inclusions, cellular and non-cellular. (*g*) The "megacaryocyte," is a smaller phagocytic cell, between which and the large lymphocyte or large mononuclear cell of the normal blood there are all stages of transition. They are smaller than the giant cell, but larger than the granular myelocytes, and have a non-granular protoplasm and a round, oval, or bean-shaped nucleus, eccentrically placed and usually with a pale stain. By most writers these cells, or at least a part of them, are thought to arise from the endothelium of the reticulum. They are by far the most actively phagocytic cells in the body. Aubertin, Dominici, and one or two other writers have reported the finding of megacaryocytes in the circulating blood, but the finding has not as yet been generally accepted. In marrow the last two varieties are present in scanty but varying numbers.

The islands of cellular hæmopoietic tissue are most numerous in the short bones and toward the epiphyses of the long bones, and grow more and more infrequent as one passes toward the middle of the bones. The younger the individual the larger the amount of hæmopoietic tissue, especially of the erythroblastic type, and the smaller the amount of fat. To this juvenile or infantile condition the marrow is prone to return when stimulated by any of a number of pathological conditions (infection, toxæmia, anæmia). We say then that the marrow has become *hyperplastic*, but this hyperplasia varies a great deal in type, according to the nature of the stimulus in response to which it is conceived to occur.

[1] It is difficult in marrow preparations to distinguish lymphocytes from young red cells and from free erythrocyte nuclei.

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In typhoid fever and in variola, for example, we find hyperplastic marrow. The degree of change varies a great deal in different cases, but the hyperplasia is made up especially of mononuclear cells with basophilic protoplasm, many of them indistinguishable from the lymphocytes of the circulating blood and aggregated into definite follicles (myelocytes, 40 to 50 per cent.; lymphocytes, 30 to 50 per cent.—Longcope). In pneumonia, on the other hand, and in most other infectious diseases attended by a polynuclear leukocytosis in the circulating blood, we find marrow hyperplasia; but this time the excess of cells is made up very largely of neutrophilic myelocytes (60 to 75 per cent.—Longcope), while their mature forms, the polynuclear cells, are quite scanty (1 to 5 per cent.), probably because they are absent on duty in the peripheral blood. The more intense and long-standing the infection, the larger the proportion of myelocytes.

Thus far the conditions found in the majority of cases have been stated, but not infrequently we find that the marrow hyperplasia occurring as a result of infectious disease involves the erythroblastic, as well as the leukoblastic, tissue. The number of red cells, nucleated and non-nucleated, begin to increase, and to assist in that crowding out of the fat which is characteristic of all the marrow hyperplasias.

In the various types of anæmia there occurs, as has already been explained, an erythroblastic hyperplasia or metaplasia of the marrow, a change which we recognize in gross by the appearance of a bright-red color in the shaft of the long bones, a color produced by multiplication of red cells, and atrophy of the yellow fatty tissue.[1] Here the following point may be added: Anæmia may give rise not merely to an erythroblastic hyperplasia or metaplasia, but also to an increase in the amount of leukoblastic tissue, that is, to a lymphoid or myeloid change. The blood may also reflect this change as in Naegeli's case of puerperal septic anæmia, in which the leukocytes were 30,000, with 25 per cent. of myelocytes. Why this occurs in some cases and not in others, and why it varies so much in degree, we cannot at present say.

The marrow changes present in the different types of leukæmia will be described later.

2. **The Spleen.**—For the purposes of this article, the most important facts about the spleen are as follows:

(*a*) In fœtal life it is the seat of red-cell formation, to which it may return under pathological conditions in infancy and occasionally in the adult.

(*b*) It plays a part in the resistance to infectious diseases. Presumably this function is more or less closely connected with that next to be mentioned.

(*c*) It is normally the seat of hæmolysis, intra- and extracellular, and of phagocytosis, so that it has been often spoken of as a "scavenger," or as a "graveyard" for defunct or superannuated red corpuscles. In disease, especially in pernicious anæmia, this function of hæmolysis becomes dangerously, even fatally, exaggerated.

(*d*) It is chiefly and essentially a lymph gland, and its Malpighian bodies correspond to the follicles of lymph glands, so that after splenectomy a compensatory hyperplasia of the other lymph glands usually occurs.

(*e*) By reason of the close connection of its origin and function with those of the bone-marrow, it is very prone to undergo metaplasia, whereby it is transformed into a tissue resembling the bone-marrow either of myeloid or

[1] "Red marrow" can also be produced by simple congestion.

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of lymphoid leukæmia. In health it seems much like a lymph gland. In disease it often reacts more like the marrow than like the glands.

(*f*) It is often the seat of chronic inflammatory processes with varying degrees of cellular hyperplasia, in which both the follicles and the endothelium of the reticulum take part. In the more chronic forms of inflammation these changes are associated with more or less fibrous hyperplasia and metamorphosis.

3. **The Lymphatic System.**—Especially important for our purpose are: (*a*) The *peripheral lymphatic accumulations* (cervical, axillary, inguinal, epitrochlear). (*b*) The *thoracic and abdominal aggregations* (tracheal, bronchial, prevertebral, mesenteric, peri-uterine). (*c*) *Those surrounding the digestive tube* (tonsillar, gastric, intestinal).

We are concerned especially with the following functions of lymphatic tissue:

(*a*) It is the source (at least according to most authorities) of the lymphocytes of the blood; the thoracic duct furnishes relatively few.

(*b*) Like the spleen, it is concerned in the resistance to infection, in the processes of hæmolysis and phagocytosis, and in the pathological hyperplasias and metaplasias.

(*c*) A varying number of the prevertebral group of glands seem to be specialized to deal with red cells as well as lymphocytes. To this group the name of *hæmolymph* glands has been given. In these glands we find, besides the ordinary lymph follicles, lymph sinuses and bloodvessels, a varying number of sinuses filled with red corpuscles. In these glands the destruction of red corpuscles, especially in pathological conditions such as infection and toxæmia, is very considerable. Whether or not these glands also take part under pathological conditions in red cell formation is a point in dispute.

Leukocytosis.—As a result probably of chemotactic influences, active especially in infectious diseases, the number of polynuclear cells in the circulating blood may become gradually or suddenly increased. This phenomenon is known as leukocytosis. This increase is made up primarily of cells summoned from the capillaries of the lung, the liver, and the sinuses of the bone-marrow, where a considerable number of these cells are normally present. If the stimulus, chemotactic or other, has continued over a considerable period, we have chronic leukocytosis, and a proliferation of neutrophilic myelocytes in the bone-marrow.

The leukocytoses have been divided roughly into *physiological* and *pathological*. Among the former the best-studied example is that occurring after violent exertion or a cold bath. As a result of these conditions, the reserve leukocytes of the lung, liver, and marrow simply shift their position and circulate in the peripheral blood. We cannot suppose that any new formation of cells occurs. There is not time. Probably of this same nature is the leukocytosis just before, during, and after parturition. In the human being there is probably no constant leukocytosis of digestion.

Pathological Leukocytoses.—(*a*) *Infectious:* As so many infectious diseases are accompanied by leukocytosis, it would be a waste of space to name them all. It is better to mention simply the exceptions, and to say that leukocytosis occurs in all infectious diseases except *typhoid fever*, *malaria*, most cases of *uncomplicated tuberculosis* except the meningeal form, *influenza* (most cases), *measles*, *mumps*, and *leprosy*.

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As to the occurrence and degree of leukocytosis in the different phases of infection, the following rules hold good in the vast majority of cases:

1. If the infection is severe and the patient's resistance good, leukocytosis is early, marked, and persistent.

2. If infection and resistance are both less marked, but fairly well proportioned one to the other, leukocytosis still occurs, but comes later, is less in degree, and ceases more quickly.

3. If the infection is one of unusual virulence, as in the so-called "*fulminating*" cases of sepsis, diphtheria, or pneumonia, no leukocytosis occurs; or the increase may be altogether a percentage increase, with no gain in the total number of circulating leukocytes.

4. Occasionally, when the infection is unusually mild and the resistance unusually good, there may be little or no leukocytosis.

In septic infections, general or local, the presence and degree of leukocytosis are dependent not upon the form of the exudate, but upon the virulence of the infection. For example, in appendicitis the presence of leukocytes is no proof of pus; a gangrenous process, without pus, may produce as early and marked a leukocytosis as a purulent one, and in the so-called "catarrhal" varieties it is the mildness of the infection rather than the nature of the exudate which causes the leukocytes to remain normal or permits but a slight increase.

(*b*) *Toxic.*—In a variety of non-infectious conditions, characterized by intoxication of one or another type, leukocytosis occurs, either regularly or in a certain percentage of cases. Thus, for example, in the more cachectic types of malignant disease we may suppose that the leukocytosis, which is sometimes present and sometimes absent, is due, when present, to the absorption of poisonous products evolved in the tumor. Other clear examples are seen in poisoning from illuminating gas, in uræmia, and in the later stages of diseases involving destruction of liver tissue (*e. g.*, cirrhosis).

The *degree of increase* seen in simple leukocytosis varies in most cases between 15,000 and 30,000 cells to the cubic millimeter. Now and then one sees counts much higher than this; 50,000 or even 70,000 are not very rare, and in a number of cases the count reached above 100,000. The most marked case thus far on record, so far as known to the writer, is that of Fletcher and Sappington,[1] in which a polynuclear leukocytosis of 134,000 accompanied a case of fibrosis of the liver and spleen (autopsy). In pneumonia, malignant disease, and occasionally in sepsis very high counts are seen.

The polynuclear cells usually make up from 80 to 95 per cent. of the total increase; the presence of this percentage increase is essential to the diagnosis of leukocytosis. Some writers have maintained that a percentage increase of polynuclear cells, even without an increase in the total number of leukocytes, has the same significance and the same diagnostic importance as leukocytosis in the ordinary sense, and with this belief the writer is inclined to agree.

Lymphocytosis.—Definition.—Absolute and relative increase in the circulating lymphocytes.

Conditions of Occurrence.—(*a*) This condition, which cannot always be distinguished from the blood of lymphoid leukæmia, is most marked and

[1] *American Medicine*, August 6, 1904

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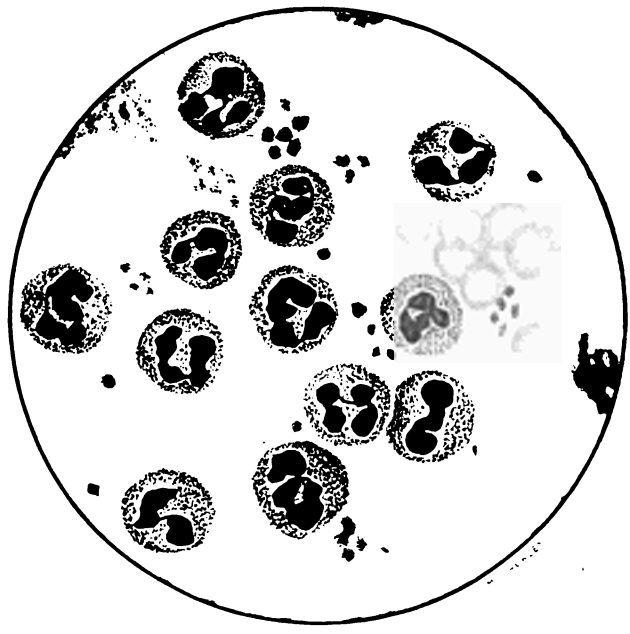
PLATE III

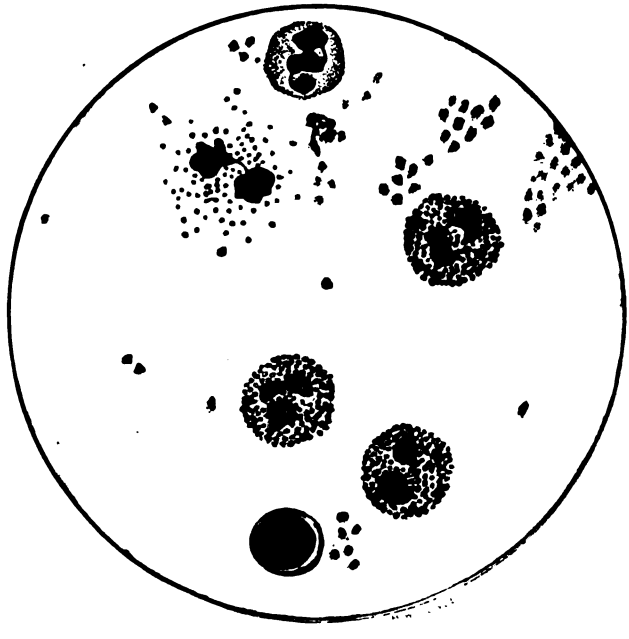
FIG. 1



Polynuclear Leukocytosis.

A reproduction of an actual field containing twelve polynuclear neutrophiles. The red cells are achromic. Blood platelets numerous.

FIG. 2



Eosinophilia (Trichinasis).

Copy of an actual field containing three normal polynuclear eosinophiles, one broken eosinophile, one polynuclear neutrophile, and one lymphocyte.

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most constant in *pertussis*. As a rule, the counts in this disease run between 20,000 and 40,000 per cmm., being at their highest in the paroxysmal stage of the disease; far higher figures have occasionally been seen. The writer's highest count was 94,000, and much higher figures have been reported by Steven.[1]

(*b*) In some cases of sepsis, especially wound sepsis with lymphatic enlargement, we may have a lymphocytosis instead of the ordinary leukocytosis. Such cases may be for a time indistinguishable from lymphoid leukæmia, but are usually recognized by their course.

(*c*) In infant's blood we have always lymphocytosis relatively to the adult. As the infant develops and its blood is approaching the adult type, any acute or chronic illness is prone to cause a return to the infantile type, with marked relative or absolute lymphocytosis.

In all the cases thus far mentioned the increase of cells is composed wholly or chiefly of the small mononuclear varieties; but in malaria and some other diseases due to animal parasites a considerable percentage of increase in the large mononuclear forms has been noted.

Eosinophilia.—Definition.—An increase in the number of circulating eosinophiles. The most important causes are as follows:

1. *Helminthiasis.*—In a large proportion of diseases due to animal parasites eosinophilia is well marked. The best-known members of this group are trichiniasis and uncinariasis. Others are filariasis, Bilharzia disease, hydatid disease, and a number of diseases due to the milder varieties of intestinal parasites.
2. Acute and chronic *skin diseases*, especially those widely distributed.
3. *Bronchial asthma.*
4. *Malignant tumors* (in an uncertain but a rather small percentage of cases).
5. Myeloid leukæmia (almost every case).
6. During the absorption of hemorrhagic effusions.
7. Ovarian disease (non-malignant and non-suppurative).
8. Postfebrile conditions.

The diagnostic value of eosinophilia is at present confined chiefly to diseases of animal parasites, and especially to the diagnosis of trichiniasis, the various intestinal parasites, and hydatid disease.

Myelocytosis.—Whenever the marrow is called upon for increased cellular production, whether the call be chiefly for leukocytes or for erythrocytes, we may find in the peripheral blood small or even considerable numbers of myelocytes. To this condition, in distinction from leukæmia, the term *stimulation myelocytosis* has been applied.

It is chiefly in leukocytosis and in anæmic conditions that the presence of myelocytes is noted. Thus, Naegeli has found 20 per cent. of myelocytes, with a total leukocyte count of 25,000 (absolute number of myelocytes 5000) in septicæmia, and the writer many times has found smaller percentages in this same disease. Any other of the causes of leukocytosis, such as malignant disease, uræmic and diabetic coma, and other toxic states, may be accompanied by myelocytosis, and Türck finds myelocytes in all acute infections, even in typhoid fever with a subnormal leukocyte count. In most cases of pernicious anæmia small numbers of myelocytes, from 50

[1] *Lancet*, September 20, 1902, vol. ii.

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to 500 per cmm. are found. In all forms of anæmia occurring in children, and especially in those accompanied by leukocytosis and splenic enlargement, myelocytes as well as other marrow elements (erythroblasts, polychromatophilic forms) are very prone to occur.

In all of the conditions above mentioned it is common to find, along with the stimulation myelocytesis, a small number of Türck's *stimulation forms* (plasma cells?).

Mast Cells.—Very little is known as to the causes which produce an increase of these in the peripheral blood, but personal observations suggest that the following generalization is true: Mast cells are increased in all the same conditions in which eosinophiles are likely to be increased, *i. e.*, in skin diseases, in helminthiasis, and in myeloid leukæmia.

Pathogenesis of the Various Types of Anæmia.—Anæmia in any of its forms represents the results of a greater or less degree of injury of the blood-forming and especially of the red-cell-forming tissues.

(*a*) **Secondary or Symptomatic Anæmias.**—In anæmias of the mildest type the red cells discharged into the blood stream are usually small, poor in hæmoglobin, and vary more than normally from the standard size. A few of them contain nuclei, or exhibit staining reactions normal for the marrow and especially for the fœtal marrow, but abnormal in the full-grown red cell. We may conceive of this type of anæmia as representing a condition in which the normal erythroblastic functions are strained to their utmost and are sending out cells in a more or less immature condition, while yet no radical change has taken place in the type of blood formation. In such anæmias we find postmortem that the erythroblastic centres have undergone hyperplasia and have crowded out the fatty marrow, so that the color in much of the tissue in the shafts of the long bones is red instead of yellow. The factory is working overtime, and has enlarged its plant; it is beginning to do more or less poor work, and to send out goods in somewhat unfinished condition. Still, it has not yet degenerated or reverted to a more primitive style of manufacture.

(*b*) **Pernicious Anæmia.**—In the type of anæmia represented by the cryptogenetic, pernicious anæmia, by fish tapeworm anæmia, and by that seen in chronic hæmolysis from accidental or experimental blood poisons, the erythroblastic centres may revert to the fœtal type, and we get what Ehrlich has termed a *megaloblastic degeneration*. Seen in gross, the marrow is usually bright red, as in ordinary secondary anæmias, but under the microscope we find that instead of the ordinary sized red cells, with or without nuclei, we have a great number of much larger cells (megalocytes), many of them nucleated (megaloblasts). It is now generally assumed that this megaloblastic degeneration is the result of an inapt and unsatisfactory attempt at regeneration, an attempt to make up somehow the losses produced by destruction of the red cells in the peripheral circulation. A call, chemotactic in nature, as is generally assumed, summons the marrow into increased and distorted activity, and the result is a hyperplasia, or still more a metaplasia, in which the place of the erythrogenetic centres is taken by cells of the fœtal type.

It should, however, be noted that the stimulus, whether chemotactic or not, does not act solely upon the red-cell-forming activities of the marrow; the hyperplasia which occurs is not wholly of erythroblastic tissue; there is also a hyperplasia of the leukoblastic portions of the marrow, so that in

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some cases the crowding out of the fat is brought about quite as much by an excess of leukocytes as by the megaloblastic metamorphosis. Some of the new-formed leukocytes find their way also into the blood stream, and when the number which are thus extruded into the bloodvessels is unusually large, puzzling clinical pictures may occur, and clinicians are sent fishing for new names, such as "leukanæmia." But the fact which should have been more fully realized ere this new term was coined is this: The stimulus, as the result of which megaloblastic metaplasia occurs, is *not strictly specific*, does not exert its influence wholly upon the erythroblastic tissue; it is to a certain extent a stimulus to the whole blood-forming apparatus, and the whole of this apparatus may respond with hyperplasia. The results of this hyperplasia are seen especially in the marrow, but also to some extent in the spleen, liver, and lymph glands, where the number of marrow leukocytes may be considerably increased.

(*c*) **Aplastic Anæmia.**—Sometimes there is no response to the call. The marrow is unable to make up the losses produced (we assume) by hæmolysis, and, instead of an increase in the bulk of erythroblastic tissue, we find an actual atrophy; that is, we find fatty marrow from end to end of the long bones, and in the peripheral blood a decrease in the granular leukocytes and a total absence of immature red cells and of cells of the fœtal types, which indicate (in other types of anæmia) that the bone-marrow is in a state of unusual, even though warped, activity.

Aplastic marrow and aplastic anæmia differ, however, only in degree, not in kind, from the type found in ordinary pernicious anæmia. In some cases considerable areas of active marrow remain in a part of the osseous system, especially in the ribs, where Naegeli found in one typical case islands of hyperplastic (retrograde-undifferentiated) marrow with 95 per cent. of marrow lymphocytes (myeloblasts) and numerous megaloblasts.

(*d*) **Myelophthisic Anæmia.**—In all the varieties above described, anæmia has seemed to be the result primarily of a destruction of the fully formed red cells, rather than of a primary failure on the part of the erythroblastic tissues. But in the type of anæmia which occurs as a result usually of leukæmia, sometimes of neoplasms involving the bone-marrow, we customarily assume that the erythroblastic tissue has been starved out, or pushed to the bony wall enclosing it, by the overgrowth of other cells, leukoblastic or neoplastic.

It is probable, however, that this process is only in part responsible for the anæmia which we find in the terminal stages of most cases of leukæmia. The accumulations of iron-bearing pigment, which we find in the liver, spleen, and lymph glands of many cases of leukæmia, suggest that hæmolysis may be in part responsible for the anæmia which we are apt to think of as a simple pressure anæmia or a crowding out of the breeding places of the young red cells.

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CHAPTER XV.

PERNICIOUS AND SECONDARY ANÆMIA, CHLOROSIS, AND LEUKÆMIA.

By RICHARD C. CABOT, M.D.

PERNICIOUS ANÆMIA (CRYPTOGENETIC).

Definition.—A chronic and usually fatal disease of unknown origin, producing, especially in elderly men, paroxysms of intense anæmia and usually degeneration of the spinal cord.

Historical.—Addison first clearly described the disease, but gave no account of its pathological anatomy. Biermer wrote a more comprehensive account of the disease, and in Germany it is often known as Biermer's anæmia. Ehrlich described the essential characteristics of the blood, with the histological details which his staining methods made possible. Since Ehrlich no one has added materially to our knowledge of the disease.

Material.—In preparing this article the writer has put together all the cases seen by him within the last twelve years, both in hospital and private practice, 337 in all. To these are added 320 collected through the kindness of my friends in different parts of this country from their unpublished records of hospital and private cases. All the cases accessible in the literature of this subject which bore the test of a critical scrutiny have been gone over, and 543 selected. All the statements of this article are based upon the analysis of these 1200 cases, together with a consideration of the easily available literature on the subject. As a rule, the two groups of cases, which are distinguished arbitrarily as "American Cases" and "Foreign Cases," show, when analyzed, substantially the same, in some items almost identically the same, results. When the divergencies are marked, both sets of figures are given in the text.

Frequency and Conditions of Occurrence.—There seems good reason to believe that the disease is not at all uncommon, nothing like so rare, for example, as leukæmia or myxœdema. At first sight one is tempted to believe that it is much commoner in certain localities than in others, but more careful study seems to show that the disease is commonest wherever it is most carefully sought; that is, in the vicinity of men who have trained themselves to recognize it. There is no reason to believe that it is any more common in New England than in other parts of this country, although at first glance the statistics might seem to suggest this. It has been suggested repeatedly that the disease is more common in rural districts than in cities, but these figures do not, on the whole, give any support to this hypothesis. Most of the writer's patients have been residents of large towns or small cities, rather than of the more sparsely settled country districts or of larger cities. The writer twice found the disease in the same family, two

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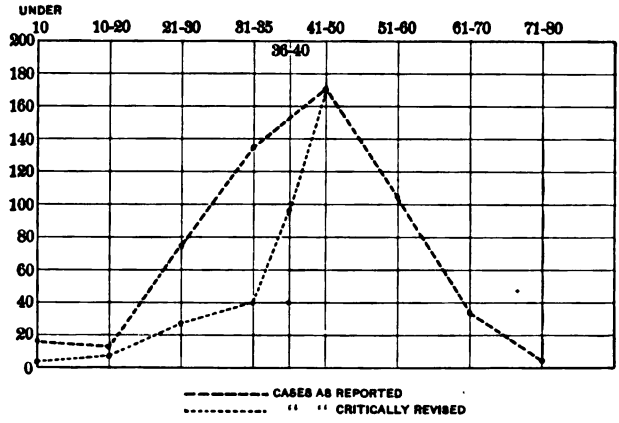
sisters being attacked in one instance, and a brother and sister in another; but the disease does not appear to be hereditary in the strict sense.

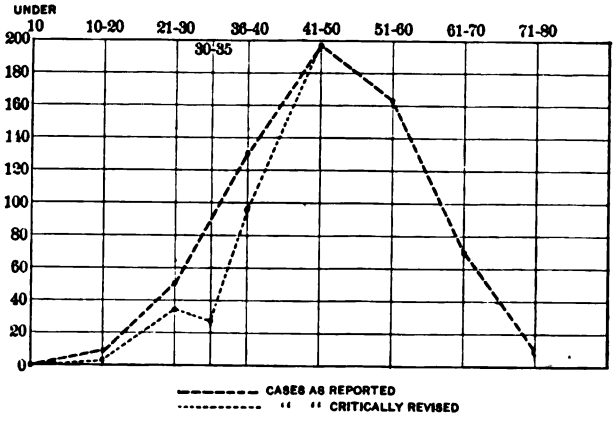
Age.—In Figs. 56 and 57 are represented the facts regarding the ages of the 1200 cases on which this article is based. A glance at these tables makes it obvious that it is a disease of elderly people, its incidence being not far

FIG. 56



Age diagram of 535 foreign cases.

FIG. 57



Age diagram of 621 American cases.

different from that of cancer. The more carefully one studies the cases, whether at the bedside or in literature, the rarer does it appear to find a typical case of pernicious anæmia before the thirty-fifth year. A small number of cases occur in the early months of infancy, but these cases are rarely typical; that is, they usually present one or more considerable divergencies from the average obtained from the analysis of any large series. In the

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decade ending with the tenth year there are less than ten well-authenticated cases on record. This figure is slightly increased in the next decade, and considerably increased in the decade ending with the thirtieth year; but in these decades (tenth to thirtieth year) the number of cases depends upon two factors: (*a*) how far back in the literature of the disease we go, and (*b*) whether we include cases originating during pregnancy or shortly after parturition. If these cases are excluded, the disease may be said to be distinctly rare under the thirty-fifth year. Even including them, more than half of all the cases collected occur between the fortieth and sixtieth years. By putting together all the cases over thirty-six years of age and all those under thirty-six years, we get the following figures: Under thirty-six years, 149, and over thirty-six years, 922, from which it appears that the disease is between six and seven times as common after the thirty-fifth year as before it. This feature has not been so strikingly manifest in the studies of the disease made previous to this time, partly because among the younger cases many have been included which do not properly belong there, such as the aplastic anæmias and those due to acute sepsis.

Sex.—Out of a total of 1157 cases available for study in this connection, 723 occur in males and 434 in females. In other words, the disease is almost twice as common in men as in women. This difference has been apparent in all the larger collections of statistics previously reported, but has never been so marked as in this one. The reason is probably the same as that just given, namely, that among the younger patients previous writers have included many (mostly women) that do not properly belong there. It is interesting to note that in the period before the thirty-sixth year the number of cases in men is almost the same as the number of cases in women—69 men and 75 women. A marked difference will be observed when compared with the figures taken from cases at all ages; that is, although *twice as common in men as in women after thirty-five*, it is *slightly commoner in women under that age*. These figures are not essentially different in the two groups of cases distinguished as "American" and "Foreign."

Race, civil condition, residence, occupation, habit of body, and time of year do not seem to have any special bearing on the disease. At one time the writer had a series of cases in the wives of physicians, but further experience has shown that this was a coincidence. Hygiene and education apparently do not make any difference in the liability to the disease.

Supposed Etiological Factors.—Some of the factors which have usually been considered in relation to the etiology of the disease may be considered.

Pregnancy and the Puerperal State.—There are 35 cases among the 1200 of this series in which the disease began during pregnancy or shortly after parturition; the more carefully we study this group of cases, the larger becomes the number of those originating during pregnancy and the smaller the number of those which began after parturition. It usually turns out that no examination of the blood has been made before parturition, so that the onset of the disease has been gauged by that very unreliable test, the appearance or complaints of the patient. The number of those originating postpartum is further reduced when we exclude those which are probably due to septicæmia and those which may fairly be classed as posthemorrhagic. Excluding these we find that 18, or slightly more than half of this group of 35 cases, originated during pregnancy. These cases are presum-

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ably to be explained as the result of hæmolysis, which in turn is in all probability a manifestation of auto-intoxication brought about by the pregnant state and manifesting itself also in nephritis, eclampsia and obstinate vomiting.

There seems to be considerable reason for separating this group of cases from the main body of those which go under the name of pernicious anæmia; for, in the first place, these cases arise at an age which we have shown to be uncommon, judging from the table of statistics; practically all of them occur before the thirty-fifth year, and the great majority before the thirtieth. Then they occurred in the sex which in general is relatively less often affected. Third, their course is much more apt to be progressive and without the characteristic remissions ordinarily seen. Lastly, they are not infrequently curable, provided their cause is removed. For all these reasons it seems best to draw a distinction between this group of cases and the larger cryptogenetic group. When the cause of this larger group is found it will probably turn out to be distinctly different from that of the cases occurring during pregnancy and after parturition.

Reference may be made briefly at this point to a case studied by the writer in 1898, because it is typical of many which have been wrongly included in the previous statistics of pernicious anæmia. The patient, twenty-two years of age, entered the Massachusetts General Hospital, March 17, 1898, for a profound anæmia, which first excited alarm three days after the birth of her third child, *i. e.*, about four and a half weeks before her entrance to the hospital. Her symptoms were the ordinary ones of grave anæmia, presently to be described. The blood showed 800,000 red cells and 22,000 white cells per cmm., with 10 per cent. of hæmoglobin. She complained of nothing that would suggest any local lesions, and, except for the marked polynuclear leukocytosis, there was nothing to distinguish the blood from that of pernicious anæmia. The leukocyte count rose gradually in the course of two weeks to 50,800. At autopsy, which occurred shortly after this count was made, we found a diphtheritic endometritis, with all the evidences of an acute sepsis. Without the autopsy this case would have been classed as one of the puerperal type of pernicious anæmia, despite the elevation of the count of white cells which is never seen in true pernicious anæmia.

Syphilis.—Only 2 cases were found, 1 among the American and 1 in the Foreign series, which present the picture of typical pernicious anæmia occurring during the course of an active attack of syphilis. All cases are excluded in which the evidences of syphilis had disappeared some years before the onset of anæmia; also 2 cases of congenital syphilis with anæmia, but not typically of the pernicious type. Some dermatologists state that cases of grave anæmia complicating syphilis are much more common on the continent of Europe than in this country. However this may be, it is not very uncommon to see anæmia of the ordinary type, later to be described as symptomatic or secondary, in the course of syphilis; but the writer has never seen a case in which pernicious anæmia, properly so called, has occurred in this connection; it is probably safe to say that such occurrence is very rare. Aside, however, from the question of the occurrence of such cases, it seems best to exclude them from the group now under consideration, because we have a definite cause and a group of clinical manifestations wholly other than those with which we are familiar in the cryptogenetic cases.

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Malaria.—There are no cases in this series in which the characteristic blood picture of pernicious anæmia developed during an attack of unquestioned malaria. Malaria is mentioned in the history of 90 cases; but in almost all of these the infection came and disappeared years before the onset of the anæmia; in none was the relation sufficiently close to suggest causation. It is true, however, that by several very competent Italian observers, and by James Ewing, in New York, the occurrence of typical pernicious anæmia in the course of malarial infection has been noted. It is most convenient to exclude these cases from the group under consideration because of the presence of a well-recognized cause. In the vast majority of cases of malaria the anæmia which develops is of the ordinary secondary type.

The Menopause.—Fifty-two cases of the 1200 occurred in close relation to the time of the menopause, but as the disease is especially prone to occur at this age in men as well as in women, and as the number of cases occurring just before the menopause is fully as great as those occurring just after it, there does not seem sufficient reason to connect the anæmia with the cessation of menstruation.

Atrophy of the Gastric Tubules.—In 61 cases atrophy of the gastro-intestinal mucosa was noted in the autopsy record; but (*a*) the lesion is very possibly due to postmortem changes; (*b*) the number of cases in which no such "atrophy" was found is also considerable; and (*c*) even were this lesion a constant one, there would be no good reason for supposing that it is the cause rather than the result of the disease which we are studying.

Gastro-intestinal Sepsis.—W. Hunter has tried to show that the pathologically increased hæmolysis of which all modern writers find convincing evidence in pernicious anæmia, has its site in the gastro-intestinal tract and its cause in sepsis, oral, gastric, or intestinal. Only in a minority of recorded cases, however, is there any evidence of such sepsis or of any connection between the gastro-intestinal tract and the hæmolysis which occurs in the marrow, spleen, glands, liver, and kidneys.

Intestinal Parasites.—No case is included in this series in which there was evidence of the existence in the body of a parasite known to be capable of producing a severe type of anæmia. It has been conclusively proved by the brilliant monograph of Schaumann that a disease identical in all respects with pernicious anæmia can be produced by the presence of the fish tapeworm (*Dibothrocephalus latus*) in the intestine, and especially by the disintegration of the segments of this worm. It is probable also that some of the many cases of severe anæmia, attributable to hookworm disease (uncinariasis), are of the pernicious type; but it has seemed best to exclude these cases from consideration in this section, because of their definitely established etiology.

The Relation of Bone-marrow to the Etiology.—It is generally agreed to-day that the changes which we find after death in the bone-marrow of cases of pernicious anæmia are the result rather than the cause of the disease, and represent an effort, more or less intense and successful, to resist the disease and to make up for the corpuscles destroyed. Here it is sufficient to say that the rare cases of anæmia due to a destruction or replacement of marrow by other tissues (bone, fibrous tissue, malignant disease) belong in a group different from that here discussed.

Chronic Diarrhœa.—In 7 of the cases analyzed in this article the evidences of anæmia were preceded and accompanied by a long-standing diarrhœa.

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In 2 cases the duration was two years, in 2, three years; in 3, five years; in 1, ten years. The histories of these cases are not known in sufficient detail to make it clear whether the diarrhœa was persistent or intermittent. It is well known that diarrhœa occurs as a symptom in the course of many cases of pernicious anæmia; and we may well doubt whether in these cases it was cause rather than result of the disease. Anæmias ordinarily seen as a result of chronic diarrhœa present a blood picture quite different from that of pernicious anæmia.

Nervous Shock.—Several writers have discussed the question whether or not the occurrence of intense mental and emotional strain, such as we find ushering in the symptoms of several of the cases in this series, is to be considered as cause or result of the disease. On the whole, the writer is inclined to believe it to be a result, inasmuch as in the vast majority of cases no such factor exists, and inasmuch as such shocks certainly occur in innumerable instances without being followed by any anæmia. There were 5 cases in this series in which such a shock had occurred.

Hemorrhage.—The type of anæmia ordinarily seen after hemorrhage bears no considerable resemblance, either in its clinical picture or in its course, to pernicious anæmia; but it seems possible that small hemorrhages over a long period of time might give rise to a true pernicious anæmia, an hypothesis which seems all the more plausible in the light of the investigations of Bunting. Nevertheless, the evidence seems to point, on the whole, strongly against the belief that hemorrhage can produce pernicious anæmia under any conditions. The writer has studied carefully 2 cases in which small hemorrhages, continued over several years, had resulted in intense anæmia, with a pallor and general appearance not unlike that of pernicious anæmia, but in both these cases the blood showed a picture absolutely different from that later to be described.

That hemorrhages occur as a symptom of pernicious anæmia is well established. In some cases they are prominent very early in the history of the disease, and in such cases one may be in genuine doubt whether he is dealing with a case of pernicious anæmia or symptomatic posthemorrhagic anæmia. As a rule, however, the amount and frequency of the hemorrhages are not such as one would expect, considering the intensity of the anæmia supposedly produced by them. Transfusion experiments show that the healthy human being will make up the loss of one or two pints of blood within a week, and in none of the cases recorded in this series have the losses amounted to anything like that quantity. Frequent nose-bleeds and long-continued bleeding from hemorrhoids were present, each of them in 4 cases of this series. One woman of thirty-two years stated that she had had frequent nose-bleeds all her life. A man aged twenty-seven made a similar statement. Yet, although it is impossible to speak with perfect assurance upon this point, it seems best to class these cases as secondary anæmia, or else to consider that the hemorrhages were symptomatic rather than causative. In any case they are rare, and should not be grouped with the other (cryptogenetic) cases of this series.

Pathology.—The evidence furnished by the condition of the tissues at autopsy suggests strongly that a powerful poison has acted upon them, affecting especially: (*a*) The blood (hæmolysis); (*b*) the spinal cord (systemic or patchy degenerations); and (*c*) the cells of the parenchymatous organs (fatty metamorphosis of the heart, liver, and kidneys).

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Presumably as the result of an unsuccessful attempt to compensate for the fearful destruction of red blood cells, there occurs a characteristic metamorphosis of the erythrogenetic tissues of the bone-marrow ("megaloblastic degeneraton"), whereby its fatty portions are largely supplanted by active blood-forming tissue closely resembling the fœtal type. The other striking result of hæmolysis is seen in the accumulation of iron-bearing pigment, especially in the liver, the spleen, and the lymph glands. These changes, together with the intense pallor of all the organs, the bright-red color of the muscles, the brilliant yellow of the fat, the frequent evidences of serous effusion, and the patchy hemorrhages on the serous surfaces, make up in outline the morbid anatomy of pernicious anæmia.

In the spinal cord, lesions have been found in 82 cases (or 84 per cent.) of those examined in this series, while in only 14 was the cord examined and found to be normal. The degenerations affect especially the cervical region of the cord, and most often the posterior columns. The roots, so far as yet examined, have shown no important changes. The systemic degenerations not infrequently extend much farther down the cord, although they are most extensive in its upper portion. In addition to this, patches of sclerosis are often found occupying the region of the lateral columns for considerable distances along the cervical and dorsal regions. It is of interest to note that similar lesions have been described in leukæmia. In the brain no important changes have been found, although in a minority of cases minute hemorrhages are scattered here and there through its substance.

Fatty degeneration is most strikingly seen in the heart muscle, and especially in the papillary muscles of the organ, where the red surface is dappled with yellow spots about the size of a pinhead or slightly larger. The appearance has been compared (most inaptly) to that of a tiger lily or of a faded leaf. In the liver and kidneys the fatty metamorphosis is often extreme. The liver is somewhat enlarged in the majority of cases and intensely yellow.

The *bone-marrow* shows the most interesting changes. (*a*) *Erythroblastic activity.* Examined in the shaft of the long bones, it exhibits in typical cases a bright-red color from one end of the bone to the other, while in consistency it is usually very soft. The red color does not in itself prove the existence of medullary hyperplasia. Congestion, as from the application of a tourniquet or from cardiac stasis, likewise produces "red marrow." Microscopic examination of smears or sections shows the presence of an unusually large number of megaloblasts, with an enlargement of the germinal centres of the erythrogenetic portion of the marrow, at the expense of all the other elements, excluding sometimes the leukocyte-forming centres and always the fat. This megaloblastic degeneration is contrasted with the normoblastic metamorphosis, which gives the bone-marrow its red color in cases of secondary anæmia.

The researches of Bunting, who produced experimentally in animals a gradual, long-standing hæmolysis by the injection of small doses of ricin, proved that a typical megaloblastic metamorphosis of the marrow can thus be produced, a metamorphosis identical with that seen in pernicious anæmia. With larger doses of this or other hæmolytic agents we get, as after experimental exsanguination, a red marrow, whose color is due not to megaloblasts but to normoblasts and normal red cells. Bunting suggests the interesting hypothesis that in pernicious anæmia we are dealing with a hæmolytic process, produced by a poison which exerts its action over a

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considerable period of time; that in an attempt to repair the damage done by this poison, the peripheral layers of the germinal erythrogenetic centres are first "peeled off," as in ordinary secondary anæmia. Then as the new-formed erythrocytes are rapidly discharged into the blood with the continuation of the hæmolytic process and the prolonged stimulation and acceleration of the blood-forming activities, the germ centres, where the large, immature red corpuscles lie, become enlarged, overactive, and finally crowd out all the other tissues of the marrow, so that immature red cells, often nucleated, and of the large type characteristic of the erythrogenetic centres, are discharged into the blood in an unsuccessful attempt to make up the losses due to hæmolysis.

If, as in cases of anæmia due to the fish tapeworm, we can remove the source of blood destruction, the marrow returns to its normal condition, functions in the normal way, and the patient recovers. If, on the other hand, as in cryptogenetic anæmia, the hæmolytic agent cannot be found or removed, the marrow grows more and more bankrupt.

An increase in the amount of iron pigment, normally deposited in the liver and to a lesser extent in the spleen, has been especially insisted upon by William Hunter as evidence that the hæmolysis, which is now generally assumed to be responsible for the disease, takes place in the gastro-intestinal tract. It has been shown, however, that when hæmolytic agents are introduced through the blood stream itself, these iron deposits occur in the same way as in pernicious anæmia of the ordinary type. We have no reason, therefore, to find in the hepatic iron deposits an evidence that the hæmolytic process takes its origin from the gastro-intestinal tract. It seems much more likely, as is now generally assumed, that the unknown poison of pernicious anæmia stimulates and pathologically exaggerates the normal phagocytic and hæmolytic activities of the spleen, lymph glands, and marrow. The pigment in the phagocytic cells and stroma of these tissues usually fails to give the iron reaction. It is in the liver and kidneys that it is changed to hæmosiderin, but the primary destructive agencies act in all probability in the hæmopoietic organs themselves.

(*b*) *Leukoblastic Activity.*—The stimulus which leads to erythroblastic hyperplasia in the marrow is presumably not specific, but exerts an influence resulting in that multiplication of the marrow leukocytes which is now recognized as a common feature of pernicious anæmia and as a point of kinship with infectious posthæmolytic marrow hyperplasias and (through pseudo-leukæmia and the atypical leukæmias) with leukæmia. Indeed, the number of nucleated red cells is rarely more than a tenth as large as the number of leukocytes. Among the leukocytes the most striking increase is in the non-granular mononuclear basophilic cells. The granular myelocytes and polynuclears are also, but less strikingly, increased. A moderate amount of phagocytosis is usually evident.

(*c*) Occasionally the bony canal is enlarged and the bone thinned.

The Spleen.—In contrast with the regenerative hyperplasia of all the marrow is the evidence of destruction (hæmolysis) or of atrophy usually found in the spleen. Sclerosis and macrophagic activity are the principal features. Spleens weighing only 50 to 500 grams are not uncommonly found. The organ is tough, brownish red, and, as a rule, remarkably poor in cells, especially in red corpuscles. Lymphocytes and large phagocytic cells make up the majority of cells discoverable amid the hyperplastic stroma

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network. Pigment, intracellular and extracellular, is abundant and stains the fibrous bands so that sometimes it can be seen with the naked eye. The more chronic the case the more sclerosis and the fewer cells.

The *lymph glands* and especially the hæmolymph glands show, as Warthin has pointed out, lesions similar in kind but less in degree when compared with those just described in the spleen.

Liver.—Besides the fatty metamorphosis already referred to, we find in the liver cells (especially around their nuclei) an abundance of iron pigment. Aubertin[1] surmises that it has been brought there from the spleen in the phagocytic cells, which are so much more abundant than red cells in the hepatic capillaries.

Co-existence of Pernicious Anæmia and Other Diseases.—Now and then in the course of an autopsy on a patient killed by cardiac disease, cerebral hemorrhage, or other affections, we find in the stomach a small nodule of malignant disease. No one supposes that in such a case the death is due to the neoplasm, or that it produced the cardiac or cerebral lesions. But if a similar nodule is found at autopsy in a case of pernicious anæmia, someone is apt to suggest that the patient's death was really due to cancer with secondary anæmia, and that the clinical diagnosis of pernicious anæmia was wrong. Now it is a well-known fact that in a small minority of the cases of gastric cancer a profound anæmia does complicate the course of the disease, but in the writer's experience and in that of most competent observers the anæmia has been distinctly different from the pernicious type.

When, on the other hand, the anæmia has been of the pernicious type, the cancerous nodule has been so small and so harmlessly situated that there has been no good reason to suppose that it played any appreciable part in the patient's sufferings and death.

The same reasoning applies to the coincidence of pernicious anæmia with varying degrees of senile atrophy of the kidney. Since pernicious anæmia often occurs in a person over sixty years of age, it is obvious that a very considerable degree of senile atrophy must now and then be found postmortem, and since the renal condition known as senile atrophy differs only in degree from chronic interstitial nephritis, it is likely that in some of the cases the condition will be called nephritis and the anæmia pronounced "secondary." Nevertheless, there is no good reason to believe that pernicious anæmia is ever the result of nephritis.

Is Pernicious Anæmia Best Called a Disease of the Blood?—So prominent are the manifestations and results of anæmia in most cases of the disease that we are apt to assume that it is only the blood that is diseased. But the following facts suggest that the poison which decimates the erythrocytes exerts its effect on other organs simultaneously: (1) In some cases the spinal cord shows evidence of disease earlier and more markedly than the blood. (2) The fatty metamorphosis of the heart, liver, and kidneys is not to be explained as a result of the anæmia. It is much more likely that the anæmia, the spinal lesions, and the fatty changes are coördinate manifestations of the same unknown poison. (3) The general symptoms, weakness, dyspnœa, etc., do not always get better as the blood improves nor worse as the blood deteriorates. In other words, they are not due solely to the anæmia.

[1] *Les Réactions Sanguines dans les Anæmies Graves*, Paris, 1905.

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Symptoms.—The onset of the disease is notoriously insidious. In only 28 out of this series of 1200 cases was there anything suggesting an acute beginning of symptoms. The great majority of patients cannot state even within six months how long they have been ill, and with many there is a vague history of gradually increasing disability, extending back for years previous to the onset of more definite symptoms. The symptom first complained of in the majority of cases is *general weakness*. This was the only symptom complained of at the onset of 12 of the 643 American cases. In 160 other cases this weakness was accompanied or preceded by one or another of the following gastro-intestinal symptoms: nausea or vomiting in 52 cases, diarrhœa in 48 cases, loss of appetite in 25 cases, indigestion in 35 cases, and sore mouth in 6 cases.

Next to the gastro-intestinal tract it is the nervous system which is most often the seat of complaints accompanying the early weakness. Thus in 49 cases of this series, headache, vertigo, blurred vision, or fainting were present at the onset. In 39 other cases a numbness, tingling, or other abnormal sensations in the hands and feet were noticed by the patient before any other symptoms occurred. In 20 patients mental symptoms, such as somnolence, nervous irritability, lack of energy or power of concentration, showed themselves earliest. In one very intelligent patient, who passed through five attacks of the disease, these mental disturbances distinctly preceded all other symptoms, including bodily weakness. In 2 cases loss of power in the legs was the earliest symptom of the anæmia developing later than the signs referable to the spinal cord.

Besides the two modes of onset already alluded to, namely, those with gastro-intestinal symptoms and those with symptoms referable to the nervous system, a smaller group is characterized by circulatory disturbances, especially dyspnœa (25 cases) and œdema (14 cases). Palpitation was also an early symptom in 8 cases. Twenty-nine patients noticed a simultaneous loss of appetite and weight earlier than any other symptom. In addition to the groups of cases already noted, there are a few unusual modes of onset to which reference may be made here. Thus, fever without any assignable cause was the first abnormality noticed in 3 cases, while in 3 others chills were among the earliest manifestations. Jaundice was the first fact called to the attention of 5 patients in this series, while in 6 hemorrhage from the nose and mouth preceded other symptoms.

Special attention should be drawn to the fact that a considerable proportion of all the patients suffering from pernicious anæmia do not look very sick, nor consider themselves very ill, when they first come under observation. Of course, there are great variations in this as in all the other portions of the symptomatology, but one of the reasons why the disease is so often unrecognized is our unwillingness to attach so ominous a name to a disease which causes in its early stages so little discomfort to the patient. This one patient, a drygoods salesman, for months worked fourteen hours a day in the basement of an ill-ventilated store, and at a high pitch of nervous tension, while suffering from pernicious anæmia, with a count of red corpuscles considerably below 2,000,000 per cmm. It had long been this patient's habit to enjoy a swim of half a mile or so each morning before breakfast, and he continued this habit for months after the disease was advanced to the point indicated by the blood count above mentioned. He usually walked to and from his work, a distance of three miles each way, at this period;

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and his muscles were like iron. Of course, this is an extreme case, but instances are not rare in which the patient showed a degree of muscular and mental power altogether astonishing when compared with the impoverishment of the blood as revealed by microscopic examination.

Color.—Of course every patient with pernicious anæmia exhibits sooner or later a very striking change of color. In the early stages of the disease this change may be very slight, especially when the color index remains high. In other cases the patient first presents himself with the classical, waxy, yellow tinge well developed throughout his cutaneous surfaces. The intensity of the yellow varies very much in different cases. In 12 cases of this series it was so intense that the term "jaundice" was applied by competent observers. In many other cases the yellowish tinge of the skin and conjunctiva is sufficient to make us hesitate a good deal before deciding whether to pronounce it jaundice or not. In another large group of cases the color of the skin does not differ appreciably from that seen in other types of anæmia, but the relatively good preservation of the subcutaneous fat layer gives the patient a different and peculiar appearance, although intense whitish pallor is, in fact, the only color change.

Another discoloration of the skin seen in 38 cases of this series, and frequently referred to in literature, is the brownish tint resembling sunburn, and usually attributable to the use of considerable doses of arsenic over a long period. Associated with this, 8 cases in our series show vitiligo or leukoderma distributed in patches here and there over the body.

In dealing with the symptoms of the established disease, after the onset is past, it seems convenient to divide them into two groups:

I. The symptoms common to all types of anæmia.

II. The symptoms more or less peculiar to pernicious anæmia.

Symptoms Found in Pernicious Anæmia and Other Anæmias as Well.—(1) Muscular weakness; (2) dyspnœa; (3) palpitation; (4) headache; (5) vertigo; (6) tinnitus; (7) anorexia; (8) œdema.

(1) *Muscular weakness* is present in practically every case as soon as the disease is well established; it was complained of by 1101 out of 1139 cases of this series. (2) *Dyspnœa* was present in 800 out of 915 cases. (3) *Palpitation* occurred in almost every case. (4) *Headache* was present in 398 out of 697 cases. (5) *Vertigo* was present in 271 out of 455 cases, or approximately 60 per cent. (6) *Tinnitus* occurred in the great majority. (8) *Œdema*, usually affecting the legs, was seen in 330 out of 572 cases (or 57 per cent.).

Symptoms More or Less Peculiar to Pernicious Anæmia.—*Gastro-intestinal crises*, or paroxysms of pain in the stomach, with or without diarrhœa, were present in 341 out of 563 (or 60 per cent.) of the American cases, and in 677 out of 953 (or 71 per cent.) of the whole series, the symptom being somewhat more common in the foreign than in the American cases. Very important in this connection is the fact that periods of perfectly good digestion occurred repeatedly in almost every case, and usually covered more than half the total duration of the illness. When the gastro-intestinal symptoms supervene, it is usually impossible to trace any cause for them; they are generally resistant to any form of treatment, and seem to run a self-limited course, leaving the patient much exhausted. Yet, curiously enough, they are often followed by a marked improvement in all symptoms.

Diarrhœa, steady or paroxysmal, occurred in 464 out of 897 cases (or practically in 50 per cent.), while in 316 cases (or 35 per cent.) there was

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constipation, and in 166 (or 15 per cent.) constipation and diarrhœa alternated.

Of special interest is the occurrence of one or another type of *sore mouth*, a symptom to which William Hunter has drawn special notice, since he believes it to be connected with the etiology of the disease. Careful note was made regarding the condition of the mouth in only 372 cases of this series. Of these, 159 showed some form of sore mouth, usually a diffuse hyperæsthesia, affecting especially the tongue, and associated with a bright-red, beefy appearance. Several of the patients complained of this symptom very early in the course of the disease, possibly before any other discomfort was felt. In other cases there were ulcerations, more or less severe, or herpetic lesions. It will be noted that the percentage of cases with sore mouth (42) is not far from that of the cases with diarrhœa (40 per cent. in the American cases; 65 per cent. in the foreign).

Symptoms Referable to Disease of the Spinal Cord.—We may divide the cases into three groups: (*a*) Those in which the symptoms of anæmia precede and overshadow those referable to the spinal cord. (*b*) Those in which the spinal symptoms appear earlier, or give rise to more discomfort, than those produced by the anæmia. (*c*) Those in which symptoms of this type are trifling or absent, despite the presence, postmortem, of well-marked lesions in the spinal cord.

In the majority of all cases of pernicious anæmia we have no symptoms that could possibly be referred to spinal disease except numbness, tingling, or other abnormal sensations in the hands and feet. These discomforts are present in almost every case, even in some of those which have shown postmortem no changes in the spinal cord. Hence, we cannot properly attribute them to any cord disease. Aside from these paræsthesias, the cases with important spinal symptoms may be divided roughly into two groups: (*a*) those in which we have a spastic gait, with increased reflexes, and a greater or less degree of paralysis, and (*b*) those in which the symptoms are strongly suggestive of tabes dorsalis, the reflexes being diminished and ataxia prominent. In this series there were 46 cases of the spastic type and 75 of the tabetic type, while in 2 cases the symptoms in the earlier part of the disease were of the spastic and later of the tabetic type. In most of the spastic cases, anæsthesia, with incontinence of urine and fæces, gradually developed. Besides these two types there is a small group (6 cases), in which the symptoms were like those of a diffuse myelitis, with complete paralysis of the four extremities and relaxation of the sphincters.

In addition to these relatively advanced and complete pictures of spinal disease, there are many cases in this series which show a variety of what might be called "fragments" of the complete clinical picture. For example, *ataxia*, or unsteady gait, with or without Romberg's symptom, was present in 25 cases. *Lightning pains* were complained of by two patients, who had no other obvious signs of tabes. *Girdle sensation* was mentioned by five and *loss of sexual power* by four. The following *paralyses* are also mentioned: of the arm in 2 cases, 1 transient; the face and one arm in 1 case; foot-drop in 1 case; hemiplegia in 3 cases, 1 of which was transient and 1 accompanied by symptoms of apoplexy; general convulsions were mentioned in 5 cases; twitching of the hands occurred in 1 case.

Sensory symptoms, with the exception of the paræsthesia above referred to, are rare. In one patient there was intense pain in all the extremities,

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and at times in the trunk, but this is very exceptional. Two patients showed pains in the arms and legs, *only on exertion*, the symptoms reminding one of intermittent claudication. Painful cramps were present in two patients, without exertion. Hyperæsthesia, usually of the extremities, was mentioned in 9 cases. In one patient the diagnosis of hemorrhage into the cord was made by a prominent neurologist.

There is no doubt that the number of cases showing one or more of the lesions above described is much larger than the statistics suggest. In the reports sent in by certain of the physicians who were good enough to allow the use of their cases there is almost no mention of spinal symptoms, while other physicians, especially those who have written upon this phase of the subject, find spinal symptoms in a large proportion of all cases, a finding, which, judging by the postmortem results, probably represents the truth.

Mental Symptoms.—In the great majority of patients there are no striking psychical abnormalities in the course of pernicious anæmia. The patient becomes gradually dull and drowsy as the anæmia progresses, and for a number of days before death may be altogether comatose; but in a small group—102 of the 647 American cases—there are interesting disturbances of mental balance. As few of the cases in the series were seen by alienists, the classification and diagnosis of mental symptoms are far from accurate.

Delirium is mentioned in 44 cases, definite delusions in 14 cases, and hallucinations in 8 cases. A "morbid psychosis," not further analyzed, was noted in 13 cases. Dementia was definitely diagnosed in 9 cases, 2 of which had been treated for a number of years in asylums for the insane, 1 for twenty-nine years. Depression of the melancholic type was mentioned in 3 cases, and mania in 3 cases. Hysteria was noted in 1 case studied by Weir Mitchell. It is interesting that in 3 of the markedly insane cases the mental symptoms preceded the manifestations of anæmia by a number of months. The antemortem coma mentioned above was prolonged in one case to two weeks. One patient complained of morning blindness, which passed off as the day wore on.

Presumably these mental symptoms are to be explained as a part of the general auto-intoxication, rather than as a result of the minute hemorrhages which are sometimes found in the brain postmortem.

Hemorrhages.—The prevalent impression that there is a strong tendency to hemorrhage in pernicious anæmia is true, provided we include the small retinal hemorrhages and the small petechiæ seen so frequently postmortem on the serous surfaces. But if we search for evidence of hemorrhages of considerable size from mucous membranes (nose, gums, stomach, rectum) or under the skin, we find them in only a small minority of the cases. In only 153 (or 23 per cent.) of the 647 American cases was there any such hemorrhage. Of the foreign cases, 29 per cent. showed gross hemorrhage. (In aplastic anæmia bleeding is more common.)

In the American cases the hemorrhages were distributed as follows: nose in 53, rectum in 54, mouth and gums in 21, skin in 15, uterus in 13, bowels in 10, stomach in 10, lungs in 2, ear in 2, and urinary passages in 2. In only 15 of these cases did the hemorrhage amount to more than a few ounces of blood. Those from the nose, the ear, the uterus, and the rectum were the most extensive. In one case the loss of a pint of blood from the left ear was the first notable symptom.

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Retinal Hemorrhages.—In the American series 238 cases were examined, and 84 (or 31 per cent.) showed hemorrhage. In the foreign series 326 cases were examined, and 236 (or 72 per cent.) showed hemorrhage. The discrepancy here is very marked and is probably due to the fact that in the foreign cases retinal examinations were made more frequently, especially in the latter months of the patient's life. In most of the American cases only a single examination (made when the patient first entered the hospital) is recorded. Probably the foreign figure, 72 per cent., is much nearer the truth. The American figures prove only that retinal hemorrhages are less common in the early stages of the disease.

Physical Examination.—(*a*) **Color and Nutrition.**—On the whole, the most striking feature in the physical examination is the scantiness of abnormal physical signs, exclusive of the changes in the blood. The yellowish color seen in the great majority of all cases which have progressed beyond the earliest stages has already been described. While this engages our attention, we are apt also to note another important fact—namely, the relatively good preservation of the fat layer, which makes the cases contrast sharply with other cachectic cases. The preservation of subcutaneous fat is usually relative, rather than absolute. That is, the patient has lost surprisingly little when we consider the duration and severity of the illness. Many of the patients, as will be seen, have actually lost weight, yet the loss is often trifling, and, as we examine the patient, we find still a considerable amount of subcutaneous fat. In 728 (or 61 per cent.) out of 1182 cases in which this point was specially noted, there was no considerable loss of weight; while in 454 (or 39 per cent.) there was loss of weight. These figures are evidently very accurate, as the percentage in the American group is almost exactly the same as that in the foreign group.

It is the combination of this relatively good state of nutrition with the pallor, such as we have learned to associate with emaciation in other diseases, that gives us our first and most characteristic impression in the physical examination of patients with pernicious anæmia.

(*b*) **The Circulatory System.**—1. *The Heart.*—In a small number of cases, 85 (or 18 per cent.) of the 468 in our series, there was demonstrable enlargement of the heart, presumably owing to dilatation. It is remarkable, on the whole, that this dilatation occurs no oftener than it does. In a few cases it is extreme, especially on the right side of the heart, so that marked tricuspid insufficiency occurs, but in the majority we find nothing of the kind. The rate and rhythm of the heart are usually not markedly abnormal. The blood pressure is very low; indeed, there are few diseases in which low records have been so often found. Readings of 60 and 80 mm. of mercury for the systolic pressure with the Riva-Rocci instrument, and a 14 cm. cuff, are not unusual. *Murmurs* were present in 857 (or 76 per cent.) out of 1123 cases in which they were carefully listened for. It is surprising to find that there are as many as 266 cases (or 24 per cent.) in which no murmurs at all were heard. One is inclined to think that there are many errors in this observation, for among the writer's 342 cases there was not one without a murmur. Among the murmurs recorded in 812 cases, 258 were audible with about equal intensity all over the præcordia, 206 were best heard at the apex, 86 at the base of the heart, 48 over the pulmonary artery, and 12 at the aortic area. In 25 cases the murmur was equally loud at the apex and in the pulmonary region. In 12 cases it was equally loud at the apex and in the

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aortic area. In 142 cases we have a record simply of a systolic murmur whose point of maximum intensity is not specified. Besides these murmurs, which are those often classed as "hæmic," "functional," or "accidental," there were 14 murmurs *presystolic in time* and heard best at the apex. In 2 of these autopsy showed no lesion of the valves; in the others there were none of the other confirmatory signs of mitral stenosis, and we may surmise that the murmur was functional in type, but there is no certainty on this point. *Diastolic murmurs* were present in 9 cases, 4 of which were shown at autopsy to be free from valvular lesions. These diastolic murmurs were probably due to that unusual elasticity of the cardiovascular system which is so often present in grave anæmias of any type.

2. *Unusual Vascular Pulsations.*—In 327 (or 42 per cent.) out of 763 cases an unusual pulsation of some of the arteries was noticed. This was especially often seen in the carotids, which are spoken of as "flapping," or violently beating. In one case reported by Edwards[1] a pulsation in the upper left portion of the chest and abdomen was so violent that aneurism was confidently diagnosed during life, although nothing of the kind was revealed at autopsy. In many other cases of this series a "collapsing pulse" is mentioned.

There is no reason to believe that these unusually noticeable pulsations of the larger arteries are in any way characteristic of pernicious anæmia. Ashford and others have called attention to similar pulsations in cases of anæmia of various grades dependent upon hookworm disease, and they are repeatedly seen in intense secondary anæmia. Since autopsy usually shows an unusual thinness and elasticity of the larger arteries, we may reasonably suppose that this is the explanation of these unusual pulsations. They may be also explainable in part by diminution in the total quantity of blood contained in the cardiovascular system, a fact pointed out some years ago by Haldane and Smith, and since confirmed by other observers. It is presumably for this reason that those who make the mistake of trying to obtain blood by puncture of a finger-tip are often unsuccessful in this disease. Blood can always be obtained with ease from the lobe of the ear.

3. *Œdema.*—Among 1019 cases, 642 (or 64 per cent.) showed manifest œdema. The percentage is somewhat higher in the foreign cases than in the American group, but the discrepancy is not marked. The œdema usually affects the legs, occasionally also the hands. Serous effusions were present in 108 (or 30 per cent.) of 357 cases in which this point was carefully studied. The chest is most frequently affected, but occasionally there is marked ascites as well. How far this œdema and these serous effusions are explainable as result of simple mechanical weakness of the heart, and how far due to some of the other and more mysterious causes of œdema, we are in no position to judge.

(*c*) **The Respiratory System.**—Beyond the dyspnœa, which has already been alluded to, and the evidence of serous effusions in one or both chests, as just mentioned, there is little or nothing worthy of note on the part of the respiratory system. A cough is rarely present, and, except on exertion, the patient experiences no difficulty in breathing. Curiously enough, the oxygen exchange, which we should suppose would be greatly diminished, is actually increased in some cases, and is rarely below the normal.

[1] *Transactions of the Association of American Physicians*, 1902, p. 182.

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(*d*) **Gastro-intestinal System.**—The conditions of occurrence of the ordinary symptoms referable to the digestive tract have been noted. Physical and chemical examination of the stomach reveals the following: There is rarely any dilatation of the stomach, and when it is present it is slight or moderate in degree. While it is true that in the paroxysmal attacks of bad digestion, with diarrhœa and vomiting, there may be well-marked motor insufficiency of the stomach, this disappears as the attack passes off, and is not characteristic of the larger proportion of the course of the disease. Chemical examination of the stomach shows, as has been pointed out by Stockton and others, that hydrochloric acid is usually absent or greatly diminished, while the digestive ferments, less often tested for, have also been found, as a rule, to be absent. Among the records of 79 cases seen by the writer in which the gastric juice was tested, only in one of this number was hydrochloric acid found in any considerable quantity. In other words, we may say it is practically always absent. This seems to hold good as well of the stages in which digestion is good as of those in which it is bad, a remarkable fact, and one which makes us think less of the importance of hydrochloric acid in digestion than we would otherwise be inclined to do. This achylia has usually been explained as the result of an atrophy of the gastric mucosa, which autopsy showed to be present in 61 cases of this series. A small group of cases, however, is on record which demonstrate that we may have complete achylia without atrophy of the gastric glands, and it is probable that this atrophy when present is usually a postmortem phenomenon.

Liver.—Demonstrable enlargement of the liver was present in 364 out of 1023 cases (or 35 per cent.) of this series (33 per cent. American and 38 per cent. foreign). There are usually no other symptoms referable to the liver, unless we include as such the slight or moderate degree of jaundice seen in some cases. Gallstone attacks have been associated in the course of 3 of the writer's cases, but this is probably a coincidence.

Spleen.—Enlargement was demonstrated in 290 out of 1045 cases (or 27 per cent.) of this series (22 per cent. American and 34 per cent. foreign). The enlargement was usually slight, the edge of the organ being just palpable below the ribs, but in perhaps 1 per cent. of the cases the organ was very considerably enlarged, reaching nearly or quite to the level of the navel.

Glandular enlargement, slight or moderate, was recorded in 123 out of 691 cases (or 17 per cent.). There is no reason to attribute to it any special significance in relation to this disease.

Several writers have referred to the presence of tenderness over the long bones in this disease, as well as in leukæmia, with the implied suggestion that it had some special connection with the disease. Personal experience, however, coincides with that of many others in showing that such tenderness is present only when there is either œdema of the part or a general hyperæsthesia. There is no reason for connecting it in any way with the changes in the bone or bone-marrow. Tenderness at the junction of the manubrium with the rest of the sternum has been recently pointed out in connection with a few cases of pernicious anæmia, as well as of leukæmia, but in the former disease it has probably little significance.

Fever.—Considerable elevation of temperature was present in 475 out of 568 cases (or 79 per cent.). This fever is sometimes continued over one or more weeks at a time, so that the diagnosis of typhoid fever has been seriously considered in two of the patients seen by the writer. As a rule, however, the

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fever is lower and more irregular than that of any of the common infectious diseases. Its presence indicates a relatively severe type of disease, or a relatively severe stage of the case. During the remissions it is absent.

Urine.—The twenty-four-hour quantity is usually about normal, sometimes diminished, but rarely markedly so. The color, contrary to the impression given by William Hunter, is usually very pale, and the pigments diminished. Albumin was present in 236 out of 506 (or 46 per cent.) of the American cases, and albumin with casts in 119 (or 24 per cent.) of the cases. The amount of albumin was usually very small, but in 11 cases it was large. Casts were present, without albumin, in 3 cases. The casts seen were usually of the hyaline and finely granular types.

Blood.—I. *Gross Physical Characteristics.*—(*a*) Haldane and Smith were the first to demonstrate that the total quantity of blood contained in the body in pernicious anæmia was markedly diminished. These observations have since been confirmed by several other observers.

(*b*) A drop of blood, as it emerges from a puncture, is often surprisingly well colored, owing to the relatively high percentage of hæmoglobin which it contains. One often says to himself, on looking at such a drop, "This cannot be pernicious anæmia," and yet finds, on further examination of the blood, that the case is a typical one. Sometimes the corpuscles and plasma divide from each other in such a way as to give the drop a streaked appearance. Possibly this fact is connected with that next to be described.

(*c*) Talquist called attention some years ago to the fact that when a drop of blood in a case of pernicious anæmia is soaked into a piece of bibulous paper, the red spot produced by the blood becomes surrounded by a pale ring, slightly but distinctly darker than the surrounding dry paper. While wet, this ring appears like colorless moisture, but as the blood-stain dries, the ring persists, and is seen to have a slight grayish tint of its own. This ring, while not absolutely characteristic of pernicious anæmia, is rarely seen in any other disease.

(*d*) The abnormal fluidity of the blood makes itself apparent as soon as a drop is drawn by puncture.

(*e*) The clot usually retracts in a normal way. It is in aplastic cases that retraction is deficient.

II. *Quantitative Changes.*—Regarding the rate at which the count of red corpuscles descends from the normal to the figure at which we find it when the patient first presents himself for examination, we can form some conjecture by studying the rate of its descent in the relapse after one of the periods of improvement, which so often occur. Judging from these data, we should suppose that it takes the blood from six months to a year to degenerate, in the majority of cases, to the point where we find it when the patient first presents himself for advice. This point was below 2,000,000 red corpuscles to the cubic centimeter in 599 (or 84 per cent.) of the 715 American cases in which there is a record of the blood, and in 393 (or 89 per cent.) out of 438 foreign cases. Obviously, then, it is the rule for a patient to get along without feeling sick enough to consult a physician throughout all the earlier stages of the disease, and until the blood has reached what we should naturally consider an alarmingly low point. It is notorious that we rarely see these cases until they are "full blown," as it were; we rarely have the opportunity to watch the beginning of the disease. At the same time the latter is not unknown, for in 20 cases of the American series the blood count

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was between 3,000,000 and 3,500,000 when the patients first consulted a physician. In the foreign series this figure is much lower, presumably because a larger proportion of hospital cases was included.

Most remarkable is the fact that in 150 of 715 American cases the patient got along without a physician until his blood had actually reached a point below 1,000,000 corpuscles to the cubic centimeter. Indeed, some of these patients do not seem nearly as sick as some of those in whom the count is above 2,000,000 or even 2,500,000, for at the onset, as in the later stages of the disease, there is no close parallelism between the blood count and the intensity of the symptoms.

The movement of the curve representing the number of red corpuscles during the remissions which are so characteristic of the disease is of considerable interest. It is very rare to find the red count rising actually to or above the normal, even when the patient is feeling perfectly well and seems to be so in every other respect. Thus in only 4 out of 192 cases of the American series, in which this point was carefully studied, did the red count rise above 5,000,000 to the cubic centimeter, and in only 30 (or 15 per cent.) did it rise above 4,000,000. From 2,500,000 to 4,000,000 usually represents the highest point reached, and 141 of our 192 cases fall within these figures.

Our interest in seeing how low the count of corpuscles may fall during life is no longer so great, since we have realized that some patients die with comparatively slight reduction in the number of red corpuscles, while others are able to do hard work despite a much greater impoverishment of their blood. Quincke's often-quoted case still holds the record with 143,000 per cubic millimeter. It is of some interest to know that this patient afterward improved greatly, and went through one of the typical remissions of the disease before she died. Two other cases with counts below 200,000 have since been reported.

If we compare the figures just reported with those seen in other types of anæmia met with in temperate climates it is obvious that pernicious anæmia differs in degree, as well as in kind, from all but a very few of the cases met in practice. There is no other disease which *often* reduces the number of red corpuscles below 2,000,000, no other disease, that is, of temperate climates. In the tropics intense anæmias, resulting from malaria, hookworm disease, and other infections, are not uncommon.

(*b*) *Qualitative Changes in the Red Corpuscles.*—The percentage of hæmoglobin, although greatly reduced, is usually relatively high; high, that is, when compared with the percentage of red corpuscles. This ratio, which is ordinarily called "the color index," is very constantly and characteristically high in pernicious anæmia.

A color index of 1 or more was present in 681 out of 920 cases of this series (or 74 per cent.). Even when the color index is below 1, it is usually so little below that figure as to contrast strongly with most other types of anæmia. This high color index, which is one of the most distinctive and characteristic features of the disease, is due no doubt to the large percentage of macrocytes or oversized red corpuscles, containing an unusually large amount of hæmoglobin.

As the disease progresses, the color index becomes higher and higher, while in the remissions it goes much lower. Thus, at the time when the count of red corpuscles was at its lowest, which may be taken as corresponding

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roughly with the worst stages of the disease, the color index was high (that is 1 or higher) in 713 out of 808 cases (or 88 per cent.). On the other hand, when the red count rises toward normal, and the patient begins to feel better, the color index is apt to fall; that is, the patient gains more rapidly in the number than in the quality of his red corpuscles, many of the newly formed cells being abnormally poor in hæmoglobin. In the American series, out of 395 cases examined with reference to this point during a remission, that is, when the red count was at its highest, 203 cases (or 51 per cent.) show a color index below 1.

Examination of the Stained Blood Film.—Although a great deal may be learned by an examination of the fresh blood, much more can be learned by making use of stained blood-film. (See Plate IV, Figs. 1 and 2.)

(*a*) *Poikilocytosis*, or variation in the shape of the red corpuscles, is usually extreme. There is no other disease in which marked poikilocytosis is so often seen. At the same time it must not be forgotten that other types of anæmia occasionally show the same thing, and occasionally one sees cases of undoubted pernicious anæmia in which the cells are very slightly deformed.

(*b*) *Size of the Red Cells.*—Careful measurements of a large number of cells usually show that the average diameter is increased, as has been abundantly proven by the studies of Capps. Although it is true that, on the whole, oversized cells predominate, there are also a great many dwarf cells, some of which are so small that they may easily escape notice, especially in the enumeration of red corpuscles with the Thoma-Zeiss instrument. *Excess of oversized* cells, and presumably an increase in average diameter, was demonstrable in 408 (or 92 per cent.) of our 444 cases in which special attention was given to this point. *It is one of the most constant and characteristic blood changes in pernicious anæmia.*

(*c*) *Abnormalities in Staining Reaction.*—Diffuse polychromatophilia was present in 284 (or 92 per cent.) of 308 cases in which special attention was paid to this point. Spots of dark-blue or blackish discoloration upon the yellow or red stained ground of the red corpuscle ("stippling") were present in 115 of 191 cases. Neither of these changes—polychromatophilia and stippling—is characteristic of pernicious anæmia, but, with the exception of lead poisoning, there is no other disease in which they are so frequently seen.

(*d*) *Nucleated Red Corpuscles.*—*Megaloblasts* were found in 671 (or 94 per cent.) of 713 cases, and absent in 42 cases. In only 21 of these 42 cases was more than one blood examination made. In other words, we may say that there were but 21 (or 3 per cent.) of the 713 cases in which it was difficult or impossible to find megaloblasts. Since the number of nucleated red cells in the peripheral circulation often varies sharply from day to day, at any one examination they may easily be overlooked. Of the 21 cases without megaloblasts, 18 are probably or certainly to be classed as anæmia of the *aplastic type.*

Normoblasts were present in all but 34 of 713 cases. The number of megaloblasts exceeded the number of normoblasts in 256 (or 60 per cent.) of 422 American cases. Of the foreign cases, only about one-quarter showed an excess of megaloblasts. This discrepancy between the two groups of cases is very possibly explainable by a difference in the definition of what constitutes a megaloblast. In most of the American cases the *abnormally large size* of the cell containing the nucleus was taken as the characteristic

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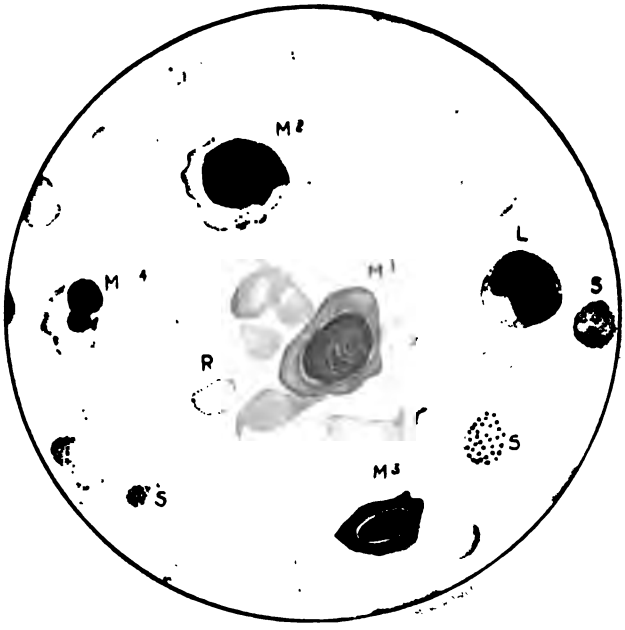
PLATE IV

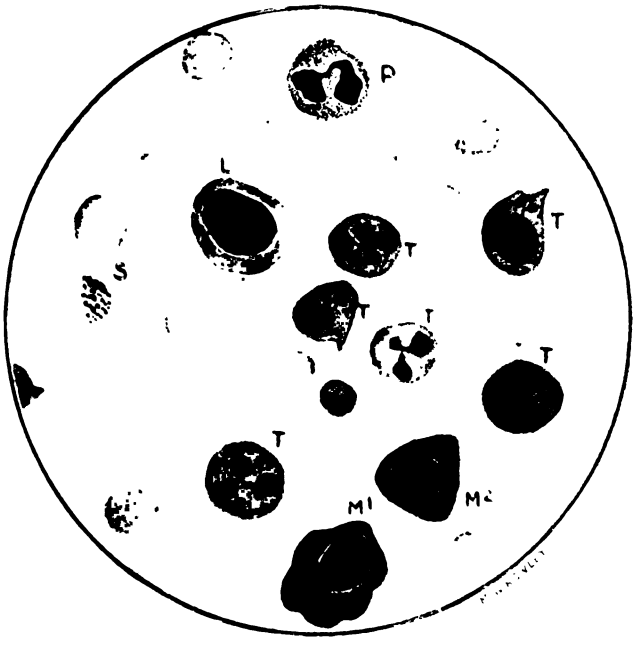
FIG. 1



Pernicious Anæmia.

The field shows marked anisocytosis and poikilocytosis; M^1, young megaloblast (early generation); M^2 M^3 M^4, later generations of the megaloblast series; *S S S*, "stippled" red cells; *R*, ring body (nuclear remnant ?); *L*, lymphocyte.

FIG. 2



Pernicious Anæmia. (Actual Field.)

Field showing less poikilocytosis than Fig. 1: M^1, young megaloblast; M^2, megaloblast of later generation; *T T T*, etc., transitional erythroblasts, not typical either of the megaloblastic or of the normoblastic series; *S*, "stippled" erythrocyte; *P*, polynuclear neutrophile; *L*, large lymphocyte.

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mark, without any regard to the size or structure of the nucleus itself. In many of the foreign cases presumably other criteria were used.

The Leukocytes.—*Quantitative Changes.*—Subnormal counts are the rule. Thus in 304 (or 56 per cent.) of 539 American cases the number of leukocytes was below 5000 per cubic millimeter when the patient first came under observation. In the remissions the number of white corpuscles rises with the number of red cells, so that in 48 of the American cases and 34 of the foreign cases the leukocyte count was between 10,000 and 15,000, and in 203 (or 54 per cent.) out of 374 American cases it was above 5000. The rise is equally marked in the foreign cases. On the other hand, at the time when the red count is at its lowest the proportion of subnormal white counts is greater than at any other time of the disease.

The *differential count* of the white cells shows a relatively small percentage of polynuclear cells and a relatively high percentage of lymphocytes. If we work out the percentages in connection with the total number of leukocytes per cubic millimeter, we find that the essential change is *a diminution in the absolute number of polynuclear cells*, while the number of lymphocytes remains at or near the normal. Lymphocytes of the smaller forms usually predominate. The percentage of eosinophiles is usually within normal limits. Occasionally, however, it is somewhat elevated, and in 83 out of 389 cases it was above 7 per cent. at some time in the course of the case. Fluctuations in the number of these cells are, however, rapid and frequent, and have no known significance.

Myelocytes in small numbers are very frequently found, and now and then reach 5 or even 10 per cent.; Aubertin has reported even higher percentages. Bearing in mind, however, the small total count of white corpuscles, we see that the total number of myelocytes is insignificant, compared even with what one often finds in ordinary polynuclear leukocytoses. Aubertin calls attention to the presence of large (marrow?) lymphocytes and of Türck's "stimulation forms" ("plasma cells"?) in cases in which myelocytes are conspicuous. He finds these forms especially at the period preceding a remission.

Blood Plates.—The number of these is usually very low. Thus, J. H. Pratt has shown that counts of 100,000 and less are not uncommon. This is not, however, the invariable rule, as the number of plates may be normal, or even increased, at some periods of the disease.

Remissions.—(*a*) **The Frequency of their Occurrence.**—Probably in the great majority of all cases the disease is not progressive, but is interrupted by one or more remissions in which the symptoms more or less entirely disappear. In only 95 (or 14 per cent.) of the 647 American cases was the course of the disease under observation a progressive one. In just 95 other cases the patients were steadily improving during the (relatively short) period of observation. But it is not at all likely that either of these groups give a fair representation of the course of the disease. Probably in most of the apparently progressive cases the fragment of the disease's course occurring under observation is, in fact, the descending portion of a wave such as is represented in Fig. 58, while almost all the cases which steadily improve under treatment until they pass out of the physician's observation are at the beginning of a remission and will subsequently relapse.

Periods in which the patient's symptoms and blood counts remain stationary for months (three, four, and nine months) are not uncommon. At the

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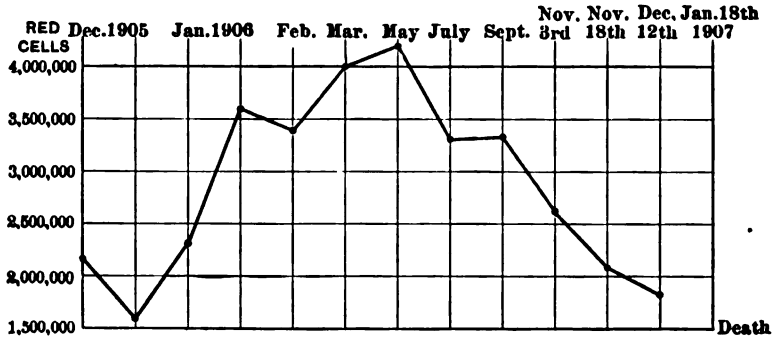
end of such a pause in the progress of the disease the patient may again be restored temporarily to (or nearly to) health, but, as a rule, this is not the case, and death puts an end to the suspense. Of the American cases, 140 were wholly stationary throughout the period of observation.

The number of remissions in a single case is often difficult to fix, for in the earlier of these waves of improvement relapse the patient does not feel sick enough to consult a physician. Only by the history can we form a rough estimate of the oscillations which have occurred. Judging in this way, we get the following results from the analysis of all the available cases:

Cases with one remission	296
Cases with two remissions	118
Cases with three remissions	65
Cases with four remissions	21
Cases with five remissions	24
Total	524
Cases observed for six months or more without any remission	159
Data insufficient for judgment as to remissions	517

FIG. 58



Typical remission in a case of pernicious anæmia.

These data are the result of inquiries and observations regarding the patient's symptoms and general condition. The curve traced by the varying blood counts during the course of the disease corresponds only roughly with the *symptom curve*. Judging by the blood counts of the American series alone, we find the following:

	Cases.
One remission in	59
Two remissions in	22
Three remissions in	8
Four remissions in	3
Course steadily downward	95
Course steadily upward	95
Course stationary	140
Died while the blood count was rising fast	5
Data insufficient	173

Sometimes the patient will improve rapidly in strength and spirits while the blood count steadily declines; occasionally the opposite occurs. Still, in the majority of cases the movements of the blood curve run fairly parallel with those of the symptom curve.

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(*b*) **Duration of Remissions.**—A study of 329 cases in which the length of the patient's respite from prostration was accurately recorded reveals the following facts:

	Cases.
Remission lasting one to three months in	79
Remission lasting three to six months in	85
Remission lasting six to nine months in	53
Remission lasting nine to twelve months in	100
Remission lasting two to three years in	8
Remission lasting three years in	1
Remission lasting four years in	2
Remission lasting six years in	1(?)

The great length of some of these remissions, as shown in this table, has not been sufficiently emphasized by other writers. When a man has been well and hard at work for two years or more, his physician is apt to think that there is no more fear of relapse. But the facts show that at any time the same unknown poison (auto-intoxication?) may again attack the tissues.

A year, as will be seen from this table, is the commonest duration for these strange pauses in the activity of the disease, and in four cases studied carefully by the writer the attack of the disease was renewed each year at the same season, sometimes in the same month. One patient had five attacks in successive years; each time the attack began in the spring, usually in March This naturally suggests the question whether any season of the year is especially dangerous or especially favorable for sufferers from this disease. The following figures, however, give no support to such an hypothesis:

	Cases.
Improvement occurred in the spring in	82
Improvement occurred in the summer in	108
Improvement occurred in the autumn in	65
Improvement occurred in the winter in	83
Total	338

Diagnosis.—When a physician is consulted by an elderly person, usually of the male sex, who complains especially of long-standing, gradually increasing weakness, with dyspnœa and marked pallor of a yellowish cast, and when on physical examination we find that the patient has lost but little flesh and presents no notable lesions in the internal organs, except the evidence of an intense anæmia and the results of this upon his cardiovascular system, then we are justified in suspecting that we are dealing with a case of pernicious anæmia.

This suspicion is confirmed and the diagnosis made positive by finding in the blood:

1. A reduction of the number of red cells to a point usually below two million per cubic millimeter.
2. A high color index.
3. A normal or subnormal leukocyte count.
4. (In he stained film-specimen). A predominance of abnormally large, greatly deformed, more or less abnormally stained red corpuscles, some of which contain nuclei.

The diagnosis is still further confirmed if the course of the disease shows one or more remissions in which the symptoms and the blood changes more or less completely disappear.

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Differential Diagnosis.—I. Defining the disease as one of wholly unknown cause, our first business in differential diagnosis is to exclude all varieties of anæmia due to well-recognized causes. This is to be done first by a careful examination of the stools to exclude *intestinal parasites*, looking especially for the eggs of the hookworm and the fish tapeworm, which are the parasites most frequently producing severe anæmia. Fortunately the eggs of these two parasites are easily and quickly recognizable in the vast majority of cases in which anæmia has been produced by them.

II. Next, we must exclude the commoner types of *secondary anæmia*, such as those due to gastric cancer, to chronic hemorrhage (as from piles), to malaria, dysentery, and the like. So far as personal experience goes, a careful study of the blood suffices to accomplish this purpose in every case. That is to say, no case of gastric cancer, of malaria, or of any of the other diseases which we know are apt to produce an extreme anæmia has been seen in which the blood was like that described above as characteristic of pernicious anæmia. In the secondary anæmias the color index is lower, the count of red corpuscles usually higher, the red cells smaller and paler in the centre (achromia); the nucleated red cells are less often of the megaloblastic type, and the number of normoblasts is relatively greater. In the experience of others, however, for example, in that of Ewing[1] and of Morse,[2] cases have occurred in which a blood picture, indistinguishable from that of pernicious anæmia, was associated with a cause, such as malaria, cancer, or hemorrhage, which we ordinarily think of in connection with secondary anæmia. In such cases our diagnosis must rest upon the evidence of these causes. Careful search must be made for a source of hemorrhage of which the patient may himself be wholly unaware, for the evidences of gastric cancer, for malarial parasites, and other possible causes of anæmia.

III. As a rule, the symptoms with which pernicious anæmia arises are unlike those of any other disease. There is nothing else which often produces in an elderly person a gradually increasing weakness, dyspnœa, and pallor, without pain and without any obvious cause. The only diseases seen in which occur a group of symptoms closely approaching those just described are *myxœdema* and *arteriosclerosis*. Myxœdema may come on with all the symptoms just described and in the same insidious way, but the type of anæmia produced is wholly different from that here described, and a careful study of the patient's mental and cutaneous symptoms will usually make the diagnosis obvious, even before the blood examination has been made. In arteriosclerosis the blood is normal. The pallor is due to the condition of the peripheral bloodvessels.

IV. *Aplastic Anæmia.*—In the group of cases which it seems best to separate (under this title) from the rest of those here described, young females predominate, nearly two-thirds of the recorded cases having occurred in women, and before the thirty-second year, that is, at an age much younger than that at which most cases of pernicious anæmia occur. The course of the disease is invariably acute, not chronic as in ordinary pernicious anæmia. Only 5 of the 24 cases in the writer's records have lasted more than three months. The course is swift and progressive to the fatal termination. Hemorrhages are far more profuse and occur in a larger number of cases than in pernicious anæmia of the ordinary type. This was the fact in 16 of the

[1] *Diseases of the Blood*, fourth edition, p. 800.
[2] *Boston Medical and Surgical Journal*, September 18, 1900.

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24 cases which were analyzed. The blood also shows marked divergencies, the most important of which are the low color index, the absence of nucleated red cells, and the high percentage of lymphocytes, 80 to 90 per cent. in most cases. These characteristics, together with a fatty, inactive marrow postmortem, are sufficient to distinguish the disease.

V. Since the spinal-cord manifestations of pernicious anæmia sometimes overshadow all others, it is not very uncommon to see cases which have been diagnosed first, and not very improperly, as tabes dorsalis or as lateral sclerosis. Only by the development and recognition of the characterstic anæmia can this mistake be avoided.

TABLE I.—DURATION OF ALL CASES (DEAD, ALIVE, OR UNTIL LOST SIGHT OF).

	American.	Foreign.
5 months	123	139
6 to 9 months	77	81
9 to 12 "	44	43
12 to 18 "	130	84
18 to 24 "	37	31
24 to 36 "	109	65
36 to 48 "	48	49
48 to 60 "	23	30
60 to 72 months and over	56	31
Total	647	553

TABLE II.—DURATION OF CASES KNOWN AS DEAD OR LIVING.

	American.	Foreign (dead).	
5 months and under	50	85	Under 1 year, 298 (many fragmentary cases).
6 to 9 months	30	74	
9 to 12 "	25	24	
12 to 18 "	60	48	1 to 3 years, 258 cases.
18 to 24 "	19	19	
24 to 36 "	62	50	
36 to 48 "	26	32	Over 3 years, 143 cases.
48 to 60 "	13	20	
60 to 72 months and over	36	17	
Total	321	379	

Cases lost sight of, 288.

Duration and Prognosis.—The course of the disease has been already sufficiently described in the section on Remissions. The duration is shown in detail in Tables I and II, where it appears that the fatal cases usually last from one to three years. On the other hand, cases not infrequently run a shorter course, so that death results within a year; while in a not inconsiderable group of cases life is prolonged three years, four years, or even considerably longer. The writer has records of 37 long cases, 10 of which lasted seven years or more, 4 for eight years or more, 6 for nine years, 9 for ten years, 3 for eleven years, 2 for twelve years, and 3 between fourteen and fifteen years. This list includes 6 *cases which the writer regards as having recovered.* These 6 cases, all in the American series, seems to the writer to have passed beyond the period when one need fear recurrence. That is to say, when a patient has been six years free from trouble, it seems safe to conclude that no recurrence will occur. This small group of cases demonstrates the *possibility* of recovery, but when we consider that there

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are but 6 cases in 1200 in which recovery is known to have occurred, the frightful mortality of the disease under our present treatment is obvious.

Treatment.—*Rest* is undoubtedly beneficial in some cases. Some patients, whose symptoms have been steadily getting worse *as long as they continue at work*, begin to improve as soon as they are put to bed, but this applies unfortunately only to the patients who have been able to persist in work, despite the increasing anæmia. To the great majority of patients for whom the disease has long since rendered work impossible, a rest-cure is wholly inapplicable, because they are already at rest.

It is probable that good hygiene, including an abundance of nourishing food and a life wholly in the open air, tends to prolong life. There is no evidence so far that any special diet has any influence upon the course of the disease. By the avoidance of nitrogenous foods we can undoubtedly diminish intestinal bacteria, but no considerable improvement in the patient's condition can be said to result. Several considerations have led to the recommendation of measures directed to clear the intestine of its contents more thoroughly than is ordinarily done by nature. Years ago the writer noticed that after the cessation of an attack of severe, almost intractable, diarrhœa patients would rapidly improve, even though no special treatment was then given. Acting upon this suggestion, he has in several cases administered laxatives to a point sufficient to produce two or three loose dejections each day. This treatment has several times been followed by a temporary improvement in all the symptoms, but his experience is not sufficiently extensive to distinguish *post hoc* and *propter hoc* in this matter.

Influenced by the finding of large numbers of anaërobic bacteria in the intestine, Herter has advocated a daily washing out of the large bowel through a high rectal tube, combining this treatment with a limitation of nitrogenous food. Time has not yet shown whether this treatment is more successful than the administration of cathartics by the mouth.

Arsenic, given in the form of Fowler's solution, or in pill, is the drug upon which the vast majority of physicians still rely. Beginning with two drops of Fowler's solution given after each meal and well diluted, the dose may be gradually increased to ten or fifteen drops three times a day, and occasionally the patient will bear even larger doses for weeks and months. One patient took seventeen drops three times a day for nearly six months. Untoward effects to be watched for are nausea and other dyspeptic symptoms; diarrhœa; itching, burning, or swelling of the eyes; brownish pigmentation of the eyes, and the evidences of peripheral neuritis. When any of these toxic effects appear the drug must be stopped until they disappear, then cautiously tried again in a much smaller dose. Occasionally patients will bear the drug better in the form of arsenous acid, $\frac{1}{100}$ grain, in pill, three times a day after food. The writer has not as yet seen any reason to believe that atoxyl, sodium cacodylate, or any other new preparations of arsenic, have any advantage over the older methods of giving the drug, not that there is any special benefit from giving it subcutaneously.

Inhalations of oxygen, ingestion of bone-marrow, and countless other remedies have been shown by the test of time to be useless. Personally, the writer finds it difficult to believe that any drug, even arsenic, has any considerable influence over the course of the disease.

Transfusion of blood from a healthy individual to a patient with pernicious anæmia is not to be recommended and should not be done.

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Aplastic Anæmia.—In the group of cases described under the title of Pernicious Anæmia only those in which there was a considerable degree of reactive hyperplasia or metaplasia on the part of the bone-marrow in response to the enormous demand for new red cells to take the places of those destroyed in hæmolysis were included. But there is a smaller group in which presumably the same unknown hæmolytic agent is at work, but in which the marrow responds very faintly or not at all. Instead of hyperplasia or metaplasia, we have *aplasia* or actual atrophy of erythroblastic tissue in the marrow. To these cases the name of aplastic anæmia has been given. It should be remembered, however, that the distinction between aplastic and metaplastic (or pernicious) types of anæmia is one of degree only. Doubtless every sort of transition between the two types exist. In the aplastic type of pernicious anæmia we find the following differences or divergencies from the ordinary picture of the disease:

1. Aplastic anæmia is a disease of young persons. Of the 24 collected cases, 18 occurred before the thirty-fifth year.

2. The number of cases occurring in women is much larger than in the ordinary type of pernicious anæmia; 14 out of 24 cases of this series were in females.

3. The disease runs a rapid and progressive course. There are no remissions, and the patient usually dies within a few months from the beginning of the attack.

4. Hemorrhages, subcutaneous, buccal, and of other sources, are much more common than in the ordinary type of pernicious anæmia. They were notable in 16 of the cases collected.

5. The blood shows marked deviations: (*a*) The color index is usually low and not high as in ordinary pernicious anæmia. In 19 cases collected it averaged 0.8. (*b*) Among the leukocytes, which are usually very scanty, even scantier than in the ordinary type of pernicious anæmia, all the granular types (polynuclears, eosinophiles, mast cells) are markedly diminished, so that we have a marked increase in the percentage of lymphocytes. In 12 cases of the series the lymphocytes averaged 72 per cent. and counts of 90 per cent. occurred in 3 cases. The polynuclear cells make up the rest; eosinophiles and mast cells are usually absent. (*c*) Erythroblasts, both normoblasts and megaloblasts, are usually absent. Occasionally a few may be found after a long search. (*d*) There is little or no poikilocytosis, anisocytosis, polychromatophilia, or stippling in most cases. (*e*) The blood platelets are always very scanty and more constantly so than in the ordinary type of pernicious anæmia.

6. *The Bone-marrow.*—Diagnosis cannot be sure without an examination of the bone-marrow, which shows that in the long bones erythroblastic tissue has quite disappeared, leaving bones filled with fat from end to end. Of course, this describes the extreme cases, and few pathologists have the energy or the opportunity to investigate all the bones of the body with such thoroughness as would be necessary to ascertain what remnants of erythroblastic tissue are here and there remaining. Ordinarily the marrow of the femur is taken as a test. If this is yellow from end to end, the case may be assigned to the aplastic type. When any cellular elements are found they are usually lymphocytes and non-nucleated red cells.

7. The spleen shows the same condition as in the usual hyperplastic type of pernicious anæmias.

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TABLE III.—APLASTIC ANÆMIA.

	Sex and age.		Onset and duration.	Hemorrhage.	Color index.	Erythroblasts.	Lymphocytes.	Total number of leukocytes.	Marrow.	Remarks.
1. Ehrlich[1]	F	21	Acute, 30 days	Purpura and uterus	?	0	83%	very low	Fatty	
2. Bloch[2]	F	63	Acute, 6 weeks	?	0.7	0	very high	3250	"	
3. Bloch[2]	F	53	?	?		0	very high	very low	"	
4. Engel[3]	F	31	Acute, 3 weeks	Stools, gums	0.4	0	90%	very low	"	
5. Evans and Halton[4]	M	36	Acute, 2 months	Nose	0.6	0	90%	2300	"	2 erythroblasts found shortly before death.
6. Hirschfeld[5]	F	28	Postpartum, 9 mos	Purpura	?	0	72%	3600	"	
7. Muir[6]	M	14	Acute, 11 weeks	Nose, stomach, skin	0.7	0	70%	7000	"	
8. Pasteur[7]	M	24	Acute, 7 weeks	Retinal only	0.9	0	74%	2600	"	
9. Zeri[8]	F	57	? 6 mos.	Nose and skin	0.7	2 norm.	numerous	3580	"	
10. Zeri[8]	M	46	? 3 mos.	?	1.3	·0	43%	2700	"	
11. Lavenson[9]	F	33	Subacute, 8 weeks	Pelvis and chest	0.6	0	70.5 %	2560	"	1 normoblast in over 1000 leukocytes.
12. Osler[10]	M	22	Acute, 12 days	Nose	1	very scanty	31%	2400	"	Very little iron pigmentation.
13. Perles[11]	M	32	Subacute, 4 weeks	Gums, larynx, retinæ	1	0	?	normal	"	
14. Hanot[12]	F	25	Acute, 14 days	0	0.8		?	?	"	
15. Silva[13]	M	12	Subacute, 3½ mos.	Nose	0.5	0	?	4960	"	
16. Schaumann[14]	M	22	Subacute, 11 weeks	0	1.2	0	?	not increased	"	
17. Dalton[15]	F	17	Acute, 5 days	Nose, ears, skin, stomach, gums	1	0	80%	3500	"	
18. Robinson[16]	F	35	Acute, 3 weeks	0	?	?	?	?	"	
19. Lesné, Clerc, Loederich[17]	M	27	Acute, 6 days	Retinæ only	1	0	85%	2400	"	"Marrow entirely inactive."
20. Rheiner[18]	F	30	Acute, 3 weeks	Uterus, skin	?	0	?	?	"	
21. Baümler[19]	F	29	Subacute, 3 mos.	0	1+	0	?	not increased	"	
22. Lipowski[20]	F	31	Acute, 8 days	Gut, vagina kidney, gums	0.4	0	90%	not increased	"	
23. Planchard[21]	F	29	Subacute, 2 mos.	0	1	0	?	not increased	"	
24. Vaques[22]	M	19	Chronic, "years"	Skin, gums, ears	1+	0	80%	6000	"	

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Other cases reported or referred to as aplastic anæmia, but not complete enough for inclusion here, in the writer's opinion, are those of Blumer, Senator, Wolff, Escherich, Kurpjeweit, Cade, Axtell, Müller, Pebram, Freshman, and Chauffard.

Myelophthisic Anæmia.—In all the types of anæmia hitherto described the part taken by the bone-marrow has been passive and secondary. It has manifested simply the evidences of attempts at regeneration (more or less satisfactory) as a compensation for the unusual destruction of red cells produced by the unknown cause of the disease. But there is another group of cases in which anæmia is due primarily to changes in the bone-marrow, that is, to a crowding out of erythroblastic tissue: (1) By leukæmic infiltration. (2) By nodules of malignant disease. (3) By fibrous or osteoid tissues.

The most common and familiar example of myelophthisic anæmia is that presently to be described as occurring in the later stages of leukæmia, when the leukæmic infiltration of the marrow has seriously reduced the amount of erythroblastic tissue, driving it literally to the (bony) wall. Much less common, indeed distinctly rare, are the cases in which myelophthisic anæmia is the result of carcinoma or osteosclerosis, which obliterates the marrow cavity of a considerable number of bones.

CHLOROSIS.

Definition.—A disease of unknown cause, occurring only in young girls, usually between the ages of fifteen and twenty-five years, and producing moderately severe anæmia.

Conditions of Occurrence.—The most remarkable fact about chlorosis to-day seems to the writer to be the very convincing evidence that it is disappearing, at any rate in the United States. From every one of the

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physicians who have been so kind in contributing cases for the preparation of this article has come essentially the same statement: "We do not see chlorosis now as we used to ten years ago." The disease seems to be dying out. It has been possible to collect less than half the number of cases which were collected from the same sources for the article on pernicious anæmia. Barely 500 cases of chlorosis can be collected from the same clinics which furnished more than 900 cases of pernicious anæmia, and more than half of these chlorotic cases originated in or near Boston. Yet in Boston, as elsewhere, the disease seems to be steadily diminishing. In the wards of the Massachusetts General Hospital in the year 1899, and in each of those preceding it, from 20 to 35 patients with chlorosis were treated. In the year 1905 there was but one case; in 1906 but two. The course of this decline is shown in Tables IV and V. Suspecting that this falling off might be due to

TABLE IV.—CASES OF CHLOROSIS AND SECONDARY ANÆMIA IN THE WARDS OF THE MASSACHUSETTS GENERAL HOSPITAL, 1898–1907.

Year.	Cases of chlorosis.	Cases in the Irish race.	Cases of secondary anæmia.	Remarks on the cases of secondary anæmia.
1898	23	11	14	
1899	35	17	34	
1900	25	13	13	
1901	14	7	13	
1902	3	1	11	
1903	4	2	18	Only 3 cases without obvious cause.
1904	4	3	24	" 3 " " " "
1905	1	0	31	" 2 " " " "
1906	2	1	14	" 2 " " " "

TABLE V.—CASES OF CHLOROSIS TREATED IN THE OUT-PATIENT DEPARTMENT OF THE MASSACHUSETTS GENERAL HOSPITAL, 1803–1907, CASE NUMBERS 1 TO 96,000.

Among the	first	10,000	cases	treated	were	24	cases of	chlorosis and	46 of secondary anæmia
"	second	"	"	"		20	"	"	40 " "
"	third	"	"	"		11	"	"	51 " "
"	fourth	"	"	"		32	"	"	41 " "
"	fifth	"	"	"		28	"	"	31 " "
"	sixth	"	"	"		15	"	"	27 " "
"	seventh	"	"	"		13	"	"	40 " "
"	eighth	"	"	"		12	"	"	30 " "
"	ninth	"	"	"		9	"	"	13 " "
"	tenth	"	"	"		2	"	"	8 " "

the fact that the patients were now treated in the dispensary instead of being referred to the wards, the dispensary records were investigated and precisely the same condition of things found there, viz., a steady diminution of the number of cases, until in the past year we have had barely a third as many as we used to have five years ago. It is difficult to explain these facts. Certainly they are not to be explained by supposing that we now call the same cases by some other name. There has been no increase, in fact an actual diminution, in the number of cases diagnosed as *secondary anæmia without any demonstrable cause*, and our system of indexing is such that if anæmia or chlorosis was connected with any other disease (*e. g.*, chlorosis *with* neurasthenia or "general debility"), the chlorosis would be separately indexed and catalogued.

Whether the change is to be explained as a result of different conditions

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of immigration—fewer Irish immigrants, for example—different conditions of domestic service, or better hygiene, the writer cannot say, but the fact seems fairly well established and most interesting.

Etiology.—There is no such thing as chlorosis in the male, that is to say, there are few cases of anæmia occurring in boys and young men, without obvious causes. Chlorosis is a disease peculiar to women, and practically to young women. Among 497 cases collected from the records of the Boston hospitals, and with the aid of physicians in different parts of this country, all were in women, and 468 (or 94 per cent.) occurred after the fifteenth and before the thirtieth year; 3 cases occurred between the twelfth and fourteenth years, and 26 cases between the thirtieth and fortieth. Cases occurring in this later decade almost always represent relapses. The statement just made implies, of course, that for the anæmias seen in women over forty we can usually assign some obvious cause, and this appears to be the case.

It is hard to avoid the conclusion that *occupation* has some relation to the cause of chlorosis. In this series of collected cases 209 occurred in girls employed in domestic service. In these figures, the cases (14 in number) occurring in cooks are separated from the 209 occurring in other domestics, simply because it has been supposed by some writers that cooks were especially subject to the disease, a theory which these figures do not in any way support; 64 cases occurred in girls who were doing their own housework, 20 in school-girls, 12 in waitresses, and 10 in nurses. In contrast with these relatively large figures, we find that only 7 cases occurred in shop-girls and 13 in factory-girls. The other occupations show even smaller figures.

Relatively few cases occur among the well-to-do. In making this statement allowance is made for the fact that the statistics are largely drawn from hospital records, and the statement is based upon the fact that relatively few cases are seen in private practice. The writer has had but 4 in his own practice as contrasted with 127 cases of pernicious anæmia seen in the same period. It is hardly credible that the occupation of the domestic predisposes to chlorosis, and it seems more likely that the occurrence of the disease is favored by the sharp change of habits and surroundings which many girls undergo at the time when they enter domestic service. While studying the cases of this series it was striking that a large proportion of them occurred in girls who had recently come to this country, and exchanged a country life for city conditions. Similar observations have been reported in Germany, where the disease seems to be frequent among girls of German parentage who have moved to the city from the country in an attempt to better their condition. Apparently we have had more cases in Boston during the past fifteen years than have been observed in any other city in this country. Thus the number of Boston cases (234 out of 361) is nearly two-thirds of the total number, although all the cases recorded at the Johns Hopkins Hospital in Baltimore, and also all those available from the larger clinics of Philadelphia, Chicago, Buffalo, and San Francisco are included. The large proportion of cases observed in Boston can be attributed to the fact that the number of recent immigrants who enter domestic service, exchanging at the same time a country for a city life, is larger in Boston than in any of the other cities mentioned. Among our cases a majority occurred in the Irish race, which ten years ago (when chlorosis was common) supplied the larger number of recently immigrated domestics.

Judging from the fact that chlorosis is confined to the female, and that

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it occurs in the period immediately after the establishment of the function of menstruation, we can hardly help suggesting that there is some immediate relation between menstruation and chlorosis, but we can go no farther. We have nothing to say as to what that relation is, or whether we are right in supposing any such relation exists. The figures suggest it; that is all we can say.

A great many "causes" have been suggested by different writers, especially in the decade immediately preceding the present one, but no one of these "causes" receives the approval of any considerable number of those who have studied the disease. Thus, Virchow's hypothesis that the disease is due to a congenital hypoplasia of the heart and bloodvessels seems incompatible with the fact that the disease can be promptly cured by the administration of iron. Meinert's observation, that gastroptosis often occurs in chlorosis, led him to suppose that this condition was the cause of the disease, but in a majority of cases the stomach is not considerably displaced, and in the remainder it may reasonably be supposed that the misplacement is the result rather than the cause of the disease. We have general muscular weakness, with laxity of the ligaments and muscles; as a part of this appears gastroptosis. An ingenious French writer called attention to the fact that slight fever and slight enlargement of the spleen is often seen in the disease, and advanced the theory that chlorosis is an infectious disease, but no infective agent has been discovered, and it seems more reasonable to explain the facts otherwise.

Many writers have called attention to the occurrence of especially poor hygienic conditions, irregular and insufficient meals, poor ventilation, and overwork as possible causes, but a study of the cases of this series does not seem to warrant any such supposition. On the whole, the hygienic conditions of domestic service, where most of these cases originated, were fully as good as those of other working girls employed in the trades, in which chlorosis is relatively rare. In the occasional cases seen among the well-to-do, poor hygiene plays no considerable part.

More plausible seems the suggestion that in some, if not in the majority, cases of chlorosis the anæmia is secondary to an unrecognized pulmonary tuberculosis. It is certainly a fact that without careful examination of the lungs we are likely to overlook some cases of incipient tuberculosis accompanied by secondary anæmia in young women. Tuberculosis may be easily overlooked, while the anæmia holds our attention and is given out as the diagnosis. But the course and altogether favorable termination of a great majority of cases, without any treatment such as would tend to cure pulmonary tuberculosis, militates strongly against the idea that chlorosis is essentially a consequence of pulmonary tuberculosis.

Early cases of hyperthyroidism (Graves' disease) are occasionally mistaken for chlorosis, and it has been supposed by some writers that chlorotic anæmia was merely a result of an unrecognized hyperthyroidism. Careful study of a large series of cases, however, does not justify this supposition.

Mental and emotional causes, homesickness, unsatisfied longings, and the like have been held responsible by some, but in relatively few cases can we trace anything of the knd. It is certainly more reasonable to suppose that these psychical manifestations are the result of a preëxisting anæmia. Without taking the space necessary to discuss the very numerous other theories, I shall close this section by stating that in my opinion we know

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nothing about the cause of chlorosis beyond the vague guesses suggested by the statistics above tabulated.

Pathology.—Very little is known as to the anatomical basis of the disease. Virchow's oft-quoted belief that hypoplasia of the heart and vascular system bears relation to the disease has been long since discredited, and no other anatomical changes have been established. Indeed, the number of recorded autopsies is insignificant. Grawitz states that he has examined the marrow in the tibia of two cases of chlorosis without finding anything abnormal.

The marked tendency to venous thrombosis shows itself most often in the legs, and does not usually cause any serious injury. But in the cerebral sinuses it is not infrequent, and is the commonest cause of death in this disease. These thrombi are probably of the infectious type. In a considerable proportion of the reported cases this was evidently the case, and that it was so in the rest is further suggested by the fact that we have no reason to assume any abnormal tendency to clotting in chlorotic blood. Outside the vessels it clots, as a rule, more slowly than normal.

Symptoms.—The onset of the disease was slow and gradual in 332 (or 88 per cent.) of our 387 cases, in which special attention was paid to this point, while in 55 (or 12 per cent.) the symptoms came on rather suddenly so far as the patients' observation could discover. There were 182 of the patients who had been aware that they were not well for a period of from one to three months before they consulted a physician; 108 had suffered between six months and a year; 72 between four and six months; 44 had not felt well from one to two years; 17 from one to three years; while 3 dated their illness back more than three years.

The earliest symptoms are usually dyspepsia and muscular weakness. Practically every patient in this series complained of weakness, and in 501 out of 504 cases dyspeptic symptoms were also prominent. Among the dyspeptic symptoms, nausea and vomiting occurred in 228 cases; 183 patients complained of lack of appetite, but in the majority the appetite was capricious or perverted, rather than deficient. Distress after eating was complained of by 66 and flatulency by 57. Epigastric pain, presumably connected with digestive troubles, was complained of by 86 patients; while 26 others spoke of pains "around the heart," which are probably to be attributed to dyspepsia in this as in most other diseased conditions.

The *morbid appetite* which has been so often referred to in connection with chlorosis was noted in 128 cases of this series. The commonest abnormality was a special fondness for pickles and sour things, with a loss of interest in all other kinds of foods. This was the case in 22 cases, while 19 other patients mentioned a special desire for sour food alone, and 18 patients stated that sweets were the only foods they cared for. Among the more definitely abnormal desires may be mentioned a tendency to eat chalk (8 cases), slatepencils (1 case), wood (1 case), leadpencils (2 cases). Sand, bird-seed, dried coffee, sulphur, and magnesia were also eaten. As we look over this curious collection of articles, we can hardly fail to be struck, as many previous writers have been, with the fact that alkalies are craved, a fact that is of interest in connection with the overacid condition of the stomach presently to be described. Curiously enough, gastric pain and pyrosis are rarely mentioned in this series. Constipation was definitely noted in 301 cases, and was probably unnoted in a much larger number. Constipation alternating with diarrhœa occurred in 3 cases.

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Turning now to *circulatory symptoms*, we find that the patients almost always complain of dyspnœa (318 cases) and of palpitation (254 cases). Œdema was noticed in 231 cases, affecting the feet and ankles in 146, the feet and legs in 37, the face in 20, the region about the eyes in 14, and the hands in 9 cases. Doubtless it is the occurrence of slight degrees of œdema which gives chlorotic patients so plump a look.

On the part of the *nervous system*, headache is by far the commonest complaint. It was mentioned in 349 cases of this series; in 72 vertigo and in 70 a ringing in the ears was also noticed. The appearance of black spots before the eyes is almost invariable, although it is actually noted in only 45 of this series. Insomnia is also more common than would be gathered from the fact that it was noted in only 64 cases of the present series. Very frequently girls speak of feeling sleepy all day, although very wakeful at night.

Pain, aside from the digestive pain above referred to, is not frequently complained of; 67 patients spoke of backache, 16 of pains in the chest, 8 of pains in their shoulders, and 10 of pains all over, while in 13 more, pain was referred to some particular spot other than those mentioned.

Menstrual disturbances are common. In 120 cases the menses were noted as absent, in 81 they were irregular, in 57 the amount of flow was increased, and in 19 it was unusually painful. Leucorrhœa was complained of by 47 patients. Von Noorden's analysis of 215 cases showed that 56 of the patients (26 per cent.) had never menstruated up to the time when they came for advice, while in 129 cases (60 per cent.) there was a considerable interval between the establishment of menstruation and the beginning of the disease.

Summing up the symptomatology, we find that the patients complain especially of dyspepsia, with more or less perversion of the appetite, of constipation, muscular weakness and shortness of breath (often with palpitation and œdema of the extremities), of headache, vertigo, tinnitus, insomnia, and various (neuralgic?) pains. The menses are suppressed, irregular, or overprofuse. All of these symptoms come on rather gradually, in the course of from three to twelve months in most cases.

Physical Signs.—Most striking is the color and general appearance of the patient, but it takes the eye of faith to see any justification for the title of the disease (χλόρος, green). If one exercises a great deal of imagination, one may possibly see the slightest imaginable tint of olive green in the shadow beneath the chin, but that is all. But to the ordinary eye, unaided by faith, the color is a yellowish pallor in brunettes and a whitish, although extreme pallor in blondes.

More important than the precise tint of the skin is the co-existence of marked pallor with a plump and apparently well-nourished condition of the tissues, especially when this combination occurs in a young girl. It is most important to bear in mind, however, that one sees now and then a girl with an unusually fresh, bright color who turns out on examination to be decidedly anæmic. There is no safety save in the habit of testing hæmoglobin as a matter of routine in every patient who consults us.

In the *examination of the chest* the most noticeable point is the presence of cardiac murmurs. Out of 220 cases of this series in which cardiac murmurs were noted, there were 112 in which murmurs were heard with about equal intensity all over the precordia. In 55 cases they were best heard at the base, in 43 at the apex, while in only 35 was it especially noted that the pul-

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monary area was the point of maximum intensity. In 24 cases the murmur was equally intense at the apex and in the pulmonary area.

In every case the murmur was systolic in time, soft and blowing in quality, and in the majority of cases it was quite intense. The *bruit de diable*, or soft, continuous humming heard by the stethoscope over the veins of the neck, was noted in 198 cases. The murmurs above described are almost never conducted beyond the præcordia, and can rarely be heard in the axilla or in the back.

Cardiac enlargement is probably more common than would be inferred from the fact that it was noted in only 94 cases of this series, but we must add at the same time that, owing to the fact that the anterior margins of the lungs are often somewhat retracted in chlorosis (lack of full, deep breathing), an unusually large area of the heart may be uncovered in a region of the second, third, and fourth left interspaces near the sternum. Pulsation often becomes visible in this area, and the hasty observer may then conclude that the heart is enlarged. The frequent occurrence of *œdema* has already been noted.

The *respiratory system* shows nothing remarkable except deficient expansion of the lungs, demonstrable upon the anterior margins, as already mentioned.

The Abdomen.—With the exception of the occasional occurrence of enlargement of the spleen and splanchnoptosis, the abdomen shows nothing abnormal. Splenic enlargement occurred in 24 cases of this series, while gastroptosis was noted in 11. Examination of the *gastric contents* after a test meal frequently shows the presence of hyperchlorhydria, but this is often fugitive, and in many cases hydrochloric acid is normal or diminished. The hyperchlorhydria is of interest chiefly because it was for so many years taken for granted that anæmia must lead to a deficiency of function, and so to a deficiency of gastric secretion. The fact that, on measuring the quantity and concentration of gastric juice, we find evidence that the gastric glands are overactive gives us one of those wholesome shocks of which medical science is so full.

The Urine.—Albumin was present in 119 cases out of 124 tested, and casts in 42 out of 80 tested. The amount of albumin was almost invariably small, the casts few and made up almost entirely of the hyaline and granular varieties. Otherwise the sediments showed nothing of importance.

Fever.—Fever, slight in degree, irregular in course, is the rule in chlorosis, and was noted in 361 cases of the present series. In the milder cases it rarely reaches above 100.5° F., and is present only for a few days at a time, but in some of the severer types of the disease fever may be present constantly for weeks. The fact that fever is so constant in this disease, and that it is attended by the same evidence of constitutional disturbance with which we are so familiar in pulmonary tuberculosis, must put us especially on our guard against the mistake of confusing chlorosis and tuberculosis.

The Blood.—Briefly stated, the main characteristics of the blood of chlorosis (which are identical with those of secondary anæmia) consist in a slight or moderate reduction in the number of red corpuscles and a much more marked reduction in the amount of coloring matter per corpuscle, without any other striking abnormality. There are records of blood examination in 361 cases. In 256 of these (or 70 per cent.) the number of red corpuscles was between 3,000,000 and 5,000,000 per cmm., a relatively mild grade of

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anæmia, while in 81 cases the number of red corpuscles was normal or even slightly above normal. Counts between 2,000,000 and 3,000,000 were found in 60 cases, and between 1,500,000 and 2,000,000 in 6 cases.

In marked contrast to these figures, which show, on the whole, only a moderate impoverishment of the blood so far as the actual number of the cells is concerned, we find that the percentage of *hæmoglobin is reduced in* 278 out of 342 cases (or *more than two-thirds*) *to less than half the normal* amount, and in 202 cases out of these 278 it ranged between 20 and 40 per cent. The ratio between these percentages and the percentage of red corpuscles (the color index) is shown in Table VI, which makes it evident that in three-fifths of the cases the color index fell below 0.5. In other words, the corpuscles contained on the average less than half the normal amount of coloring matter. This is the essential feature of the blood picture.

TABLE VI.—BLOOD IN CHLOROSIS AT THE TIME OF ENTERING THE HOSPITAL.

Red cells.	Cases.	Leukocytes.	Cases.	Hæmoglobin.	Cases.	Color index.	Cases.
1,500,000 to 2,000,000	6	2,000 to 5,000	80	10 to 20%	26	0.1 to 0.3	24
2,000,000 to 2,500,000	22	5,000 to 10,000	184	21 to 30%	103	0.3 to 0.5	167
2,500,000 to 3,000,000	38	10,000 to 15,000	57	31 to 40%	102	0.5 to 0.8	131
3,000,000 to 3,500,000	61	15,000 to 20,000	7	41 to 50%	76		
3,500,000 to 4,000,000	81			51 to 60%	39		
4,000,000 to 4,500,000	65			61 to 70%	6		
4,500,000 to 5,000,000	49						
5,000,000 to 6,000,000	37						
6,000,000 to 7,000,000	2						
Total	361		328		352		322

The *white cells* show very little of interest; in 264 out of 311 cases their number was normal or sub-normal; in the remaining cases, elevations above normal were moderate, of short duration, and probably referable either to complications or to special physical or emotional strain at the time of the examinations.

The *stained specimen* is very characteristic, especially when contrasted with the appearances in pernicious anæmia. The average diameter of the cells is usually reduced and never increased. Their shape is usually normal; if deformities are present they are rarely considerable. Marked poikilocytosis, such as is seen in almost every case of pernicious anæmia, has never been seen by the writer in chlorosis, and there are very few records of such a condition. Abnormalities of staining reaction are not often seen, but in the severest cases, we occasionally find either polychromatophilia or stippling. The latter condition I have seen but twice. Nucleated red corpuscles are rare but not invariably absent. Eight cases of the present series showed them, although in moderate numbers. In each case they were of the normoblast type.

The differential count of leukocytes was normal in 35 of the 56 cases of this series in which it was made. Only 8 showed marked percentage increase of lymphocytes. The number of eosinophiles is occasionally increased, but it is not possible to correlate the occurrence of this condition with any special type or grade of disease.

One of the most interesting facts about the disease, first demonstrated by

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Haldane and Smith, although previously suggested by several German writers, is the marked increase in the amount of blood plasma (polyplasmia), whereby the vessels are constantly overfilled and the total amount of circulatory fluid decidedly increased. What this serous plethora may have to do with the other symptoms of the disease is as yet wholly a matter of speculation, but it is certainly a most impressive fact. *Venous thrombosis* occurred in 11 cases among the 504 here analyzed. This represents approximately the same percentage (2.2 per cent.) as in v. Noorden's 230 cases (2.1 per cent.). In this series, as in his, the extremities, and especially the legs, were involved. There was no instance of thrombosis involving the *cerebral sinuses*, such as have been reported as a cause of death by several writers.

Course and Duration.—In a considerable proportion of the cases the patient is attacked more than once. Thus, 78 of this series had already had previous attacks, and it is to be presumed that in many others the disease pursued the same course, although relatively few could be followed. More than half of those whom we were able to follow relapsed at least once before regaining permanent good health. How often these relapses would occur if the patient persisted in carrying out the treatment for months as well as for the first few weeks it is impossible to say.

Under treatment the disease is usually so far relieved that the patient is able to go back to work and feel nearly, if not quite, well *within six months;* indeed, within three months 186 of our cases had returned to work. In only 16 per cent. of cases were symptoms prolonged beyond a year. The rapidity of gain varies a good deal, but, as a rule, a patient will gain 5 per cent. of hæmoglobin every ten days if the treatment is steadily and effectively carried out. The writer has known but 3 of the so-called "obstinate cases" which resisted treatment for months.

Differential Diagnosis.—The diseases for which chlorosis is most likely to be mistaken are neurasthenia, pulmonary tuberculosis, the anæmias symptomatic of malaria, hemorrhage or other well-known causes, nephritis, and hyperthyroidism.

Neurasthenia may be excluded by the blood examination, since there is no anæmia in the vast majority of neurasthenic patients. It is, of course, possible for the two diseases to co-exist. *Tuberculosis* is to be excluded by a rigorous and searching examination of the lungs, and in cases of doubt by the injection of tuberculin. As a matter of fact, few cases of recognized incipient tuberculosis have any considerable degree of anæmia. A careful examination of the urine and of the cardiovascular system should suffice to exclude nephritis. In hyperthyroidism the pulse is more persistently and more decidedly elevated, tremor is much more marked, and either the eyes or the thyroid gland should show prominence.

Treatment.—Chlorosis is one of the four or five diseases now known to us which can be cured with a drug; despite some hypercritical skeptics, there is no longer the slightest doubt of this fact. In any case of supposed chlorosis which does not yield readily to iron administered in the proper manner and in the proper dose, we have reason for doubting the diagnosis. The drug treatment of the disease will be first discussed, for this seems even more important than diet or hygiene.

By the consensus of observers in all parts of the world, it seems now settled that the time-honored combination of sulphate of iron and potassium carbonate, in the form of Blaud's pill, is the best remedy for chlorosis.

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Other forms of iron may accomplish the desired result, but none so frequently, so quickly, or with so little disturbance of the body functions. The drug should be given in the form of the official five-grain pill (0.3 gm.), beginning with one pill after each meal, increasing at the end of a week to two after each meal, and at the end of two weeks to three after each meal. Rarely does a patient experience disturbances of the stomach or headache with vertigo after taking iron in this form. In most of these cases the drug may be given in the form of *ferrum reductum*, 1½ to 3 grains (0.1 to 0.2 gm.), in pill form after each meal. For the claims advanced for the so-called "organic" preparations of iron there is no theoretical basis, and they do not in fact work any better than the cheaper and more old-fashioned forms advised above.

While it is a fact that patients will recover fairly quickly as a result of the administration of iron without any change in their habits, and while it is also true that patients will improve without the administration of iron, provided we correct their constipation and improve their general hygiene, it was proven to the writer ten years ago, by the studies of C. W. Townsend, that the *combination of iron* administered as above *with proper hygiene*, including the treatment of constipation, results in a cure far more speedy than can be obtained either by iron alone or by hygiene alone. As a rule, constipation is best treated by the administration of cascara sagrada, 25 drops of the fluid extract at night, or 2 to 4 grains (0.13 to 0.26 gm.) of the solid extract in pill. If anorexia is present, a bitter tonic should also be given. Under this plan of treatment the vast majority of all patients promptly recover, but the patient should persist in the use of iron for at least six months after complete recovery, and should return to its use whenever there are any indications of relapse.

Now and then cases occur which resist this treatment, and which improve only after they have been kept in bed continuously for a number of weeks. In some of these, recovery is hastened by the administration of arsenic in the form of Fowler's solution, beginning with two drops well diluted, after meals, and increasing until we are warned by discomforts in the eyes or the gastro-intestinal tract that we have reached the limit of toleration. It is probably true that in some of these obstinate cases recovery may be hastened by the bleeding treatment suggested a number of years ago in Germany, but so far this measure has not found favor in this country. Several weeks of rest in bed, on the other hand, is a most valuable aid in the treatment of all severe attacks.

SECONDARY (OR SYMPTOMATIC) ANÆMIAS.

All cases of anæmia due to a well-recognized cause are conveniently classed as secondary. A characteristic blood picture accompanies most cases of secondary anæmia, but it is not possible to make this blood picture the distinguishing mark of the disease, because (*a*) the same blood picture is seen in chlorosis, and (*b*) some types of secondary anæmia (*e. g.*, those due to intestinal parasites, or to the accidental or experimental ingestion of blood poisons, such as nitrobenzol or ricin) show the blood picture of pernicious anæmia.

In a general way it may be said that the great majority of secondary

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anæmias are mild and that the blood picture associated with them is that of a relatively mild anæmia, but to this rule also there are exceptions. Secondary anæmias—due to hemorrhage, cancer, hookworm disease—may be fatal, although the blood picture remains throughout essentially of the secondary type. On the other hand, some mild stages of pernicious anæmia are associated not with a mild, but with a recognizably *pernicious* type of blood. Hence the *presence of a clear cause remains our only reliable criterion for the recognition of secondary anæmia.* Such causes are:

1. *Hemorrhage.* Extensive bleeding is most often traumatic or operative, pulmonary (phthisis), gastric (peptic ulcer, hepatic cirrhosis, splenic fibrosis, gastric cancer), uterine (owing to miscarriage, fibroid tumors, extra-uterine pregnancy, etc.), intestinal (typhoid fever, dysentery, hemorrhoids), renal (stone, nephritis, neoplasm), vascular (aneurism), subcutaneous and submucous (leukæmia, purpura, scurvy).

2. *Hæmolysis,* due to (*a*) infections; (*b*) neoplasms; (*c*) blood poisons (potassium chlorate, nitrobenzol, etc.); (*d*) auto-intoxication (uræmia, "cholæmia," pregnancy); and (*e*) intestinal parasites.

Symptoms.—Since the symptoms are essentially identical with many of those seen in the primary anæmias, the reader is referred to the sections on chlorosis and on pernicious anæmia for detailed descriptions. Here it is sufficient to classify the symptoms according as they are produced by functional insufficiency (irritation or weakness) of: (*a*) *The nervous system:* headache, vertigo, faintness, tinnitus, muscæ volitantes, vasomotor disturbances, psychic irritability or weakness, insomnia, fever (?). (*b*) *The gastro-intestinal system:* anorexia, dyspepsia, nausea, vomiting, constipation. (*c*) *The circulatory system:* dyspnœa, palpitation, arhythmia, œdema, serous effusions. (*d*) *The genital system:* amenorrhœa, menorrhagia, impotence.

Acute and chronic forms of secondary anæmia may be distinguished. Acute anæmia is due usually to (*a*) hemorrhage, (*b*) sepsis, (*c*) malaria, (*d*) blood poisons, all causing hæmolysis.

Any of these causes may produce death from anæmia within ten days. Some comment on each may be here introduced.

Acute Posthemorrhagic Anæmia.—The loss of even 50 to 70 cc. of blood produces demonstrable alterations in the corpuscles, *i. e.*, an anæmia, although the patient is usually free from symptoms. The *rapidity* with which blood is lost has as much to do with the severity of the symptoms as the *amount* lost, for the patient suffers not so much from the loss of blood cells as of blood *fluid.* Hence, when there is loss of a quart of blood in small quantities, with intervals of hours or days between the hemorrhages, the vessels are each time refilled by fluid absorbed from the other tissues and (ultimately) by fluid ingested to quench thirst. Such hemorrhages, although they may produce anæmia, cause the patient relatively little distress, because most posthemorrhagic suffering is due to empty vessels and the resulting feebleness of the heart's action, all of which is prevented when the hemorrhages are so spaced that the system has time to make up the loss not of cells but of plasma.

The regeneration of the cellular contents of the blood is sometimes slow, sometimes astonishingly rapid, the rate depending apparently upon the regenerative powers of the system focused in the erythroblastic marrow. As the body of an animal reacting to immunizing injections comes at last

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to the rapid production of very large amounts of antibodies, so the marrow, stimulated into hyperplasia and superactivity by repeated hemorrhages, acquires in many cases the power to make up the losses with wonderful rapidity. Thus in a case of cirrhosis of the liver the third gastric hemorrhage of over a quart was made up more rapidly than the first one (a pint only), because the interval of ten days elapsed between each two hemorrhages and the marrow (doubtless) was hyperplastic. So in malaria, although the number of red cells destroyed is sometimes at least 1,000,000 per cmm. by each new generation of parasites (*i. e.*, by each paroxysm), the development of anæmia may be very slow because there is time in the onset of the disease for regeneration hyperplasia.

The principal factors governing the regeneration of red cells after hemorrhage are: (*a*) The amount of time allowed for the stimulation of regenerative activity in the marrow. (*b*) The general vigor of the body. In persons whose general powers of reaction are weakened by chronic diseases such as nephritis, neoplasm, scurvy, or by lack of food, as in gastric ulcer, regeneration after hemorrhage may be slow and imperfect. Some imperfection, indeed, there almost always is. The new corpuscles are seldom as good as the old, even when their number is kept up to normal. The nature of the imperfections will be described below in the section on the blood changes.

Animals usually do not survive the loss of one-half or more of their total blood by hemorrhage. Men apparently bear hemorrhage somewhat better than most animals, but no exact limit can be stated beyond which no further bleeding can be borne. Patients whose hæmoglobin has fallen as low as 11 per cent. (Hayem) have nevertheless recovered. Patients who do not die at once as a result of a single huge hemorrhage sometimes react for a few days and seem on the road to recovery, then "go into a decline" and fade out in the course of a few weeks.

The Blood.—Immediately after a hemorrhage, at the time when we wish especially to estimate its amount from the resulting impoverishment of the blood, there is no appreciable change in the single drop which we draw for examination. It is only after forty-eight hours or more that by the restitution of the volume of plasma some degree of anæmia becomes evident, but even then its degree does not accurately represent the amount of blood lost, for the amount and rapidity of reproduction in the bone-marrow varies enormously in different cases.

The earliest changes are usually more evident in the stained specimen than in the count. Achromia, with slight variations in the size and shape of the cells, slight abnormalities in staining reaction, and an occasional normoblast are usually the earliest abnormalities of red-cell formation expressed in the peripheral blood; but since the stimulus, as a result of which regeneration occurs, acts not specifically on the erythroblastic tissue alone, but involves the whole marrow to a certain extent, we find both in the marrow and the circulating blood an increase of leukocytes. In the marrow it is chiefly the myelocytes and large mononuclear, non-granular, basophilic cells (lymphocytes?) that are increased. In the peripheral blood it is chiefly an increase, relative or absolute, in the polynuclear neutrophiles. With this we find, in most marked cases, a small number of Türck's stimulation forms and granular myelocytes.

A low color index is present in all except the severest cases; that is, the quality of the new-formed cell is inferior to the normal, even though the

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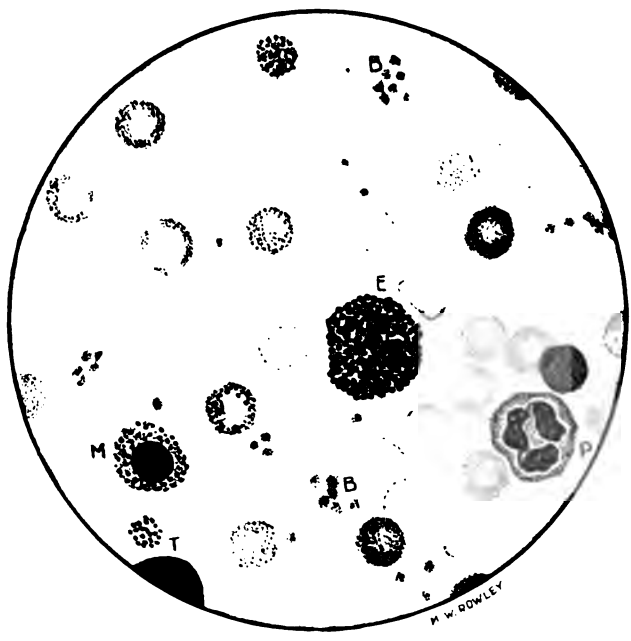
PLATE V

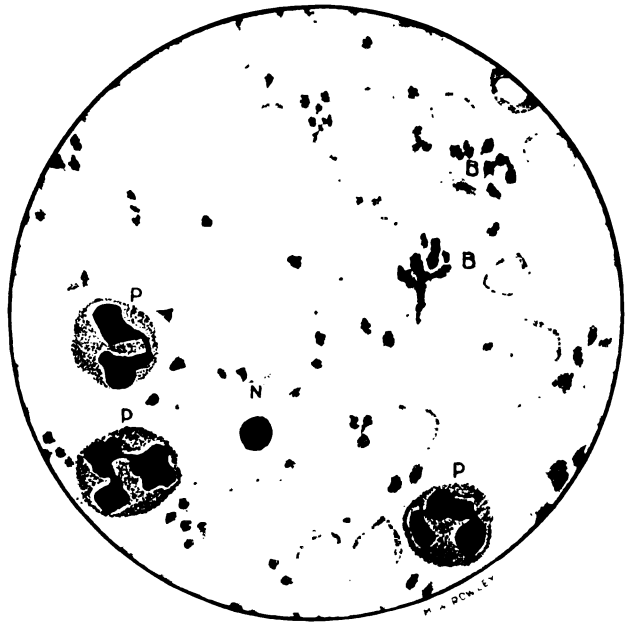
FIG. 1



Atypical Staining Reactions in Lead Poisoning. (Actual Field.)

Field shows "stippling" of various degrees and types without any marked achromia, poikilocytosis, or other sign of anæmia except *M*, stippled megaloblast; *E*, eosinophile (polynuclear); *P*, polynuclear neutrophile; *T*, Türk "stimulation form" (plasma cell ?); *B B*, blood platelets (increased in number here).

FIG. 2



Secondary Anæmia with Polynuclear Leukocytosis. (Gastric Cancer).

The hæmoglobin was 10 per cent. (Fleischl); pallor of the centres of the red cells (achromia) is striking: *N*, normoblast; *P P P*, polynuclear neutrophiles; *B B*, blood plates.

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marrow may have succeeded by unusual activity in keeping the total number of red cells somewhere near the normal. The total number of red cells is usually between 2,000,000 and 4,000,000, and the color index approximately 0.5. The wave of leukocytosis (polynucleosis) which accompanies the development of anæmia in most cases and disappears with the disappearance of the anæmia brings the number of circulating leukocytes up to a point usually between 13,000 and 18,000 per cmm.

Summarizing the blood picture of the vast majority of cases of post-hemorrhagic anæmia, we find moderate oligocytosis with polynucleosis, low color index, marked achromia, polychromatophilia, poikilocytosis, anisocytosis, a few normoblasts, and a few marrow leukocytes. This description of the blood picture after moderate hemorrhage is typical of all the other types of moderate severe secondary anæmia, such as are produced by infectious diseases, neoplasms, toxæmic states, and blood poisons.

In the severest cases, after repeated hemorrhages of large amount, the blood picture is entirely different. Thus, for example, in a case of splenic anæmia, recently seen, the patient had lost 3000 cc., or approximately three quarts, of blood within forty-eight hours. About two weeks later the blood showed 700,000 red cells, 1000 white cells, and 10 per cent. hæmoglobin. In the stained specimen there was no achromia; on the contrary, the cells were mostly oversized and as much deformed as in the average case of pernicious anæmia. There were no megaloblasts present, but with that exception the blood might have passed for that of pernicious anæmia. In the regeneration, after hemorrhages of this sort, the blood gradually returns to the achromic type with low color index, described above as characteristic of the milder grades of anæmia.

Differential Diagnosis.—Since hemorrhage may be a symptom as well as a cause of anæmia, we need to rule out pernicious anæmia and leukæmia, which might possibly be confounded with simple posthemorrhagic anæmia. This is usually not difficult, for in pernicious anæmia extensive hemorrhage, enough to produce marked anæmia, practically never occurs in the early stages of the disease; hence, in the history we should have evidences of anæmia preceding the occurrence of hemorrhage. Leukæmia may be easily excluded by the blood picture. In the hemorrhagic diseases, such as purpura, hæmophilia, and scurvy, the anæmia is essentially of the post-hemorrhagic type, and no differential diagnosis is therefore necessary.

Prognosis.—In cases of very severe hemorrhage, if efficient treatment can be secured—that is, if transfusion by Crile's method can be quickly and efficiently done—the prognosis should be good in every case, no matter how great the hemorrhage, provided that the patient's strength is not already exhausted by some underlying disease, such as leukæmia, uræmia, or cirrhosis of the liver. If transfusion cannot be done, the infusion by physiological salt solution, subcutaneously or intravenously, is the best substitute.

Treatment.—Aside from the measures just suggested for restitution of the loss of blood, nothing but careful feeding and good hygiene is necessary. The writer is not convinced that iron and arsenic hasten the process of regeneration, but if the stomach is in good condition there is no objection to their use. The subcutaneous injection of the citrate of iron in liquid form has not in my hands succeeded in aiding the recovery of the patient.

Acute Septic Anæmia.—It is not generally realized that there is any type of acute anæmia except that due to hemorrhage. The primary anæmias are

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always chronic, and the same is true of the ordinary varieties of secondary anæmia. But as a result of virulent septicæmia, such as is now and then seen after childbirth and in other conditions, the red cells may be reduced below 1,000,000 within a few days; thus Grawitz has reported a case in which the red cells fell to 300,000 in less than twenty-four hours. It should be said, however, that in this case there was postpartum bleeding as well. Several cases are on record in which a few days of acute sepsis have brought the red cells below 1,500,000. This point seems one of importance, as it is often assumed by clinicians that an anæmia of this grade could not have been produced in a few days without hemorrhage.

No doubt the destruction of red cells is the result of hæmolysis in these cases, an explanation which is suggested not only by the evidences of jaundice and the changes in the urine, but also by the results of experimental hæmolysis, to which reference will be made in the next section. Occasionally similar acute hæmolytic anæmia may result from an intense malarial infection.

Blood Poisons.—As a result of the ingestion, accidental or experimental, of hæmolytic agents, such as nitrobenzol, potassium chlorate, or ricin, very severe, usually fatal anæmias may develop. The type of blood change depends upon the nature and dose of the poison; some of the acutely fatal anæmias produced by acetanilide or by nitrobenzol have been associated with a blood picture very much like that of pernicious anæmia, although usually, as an acute sepsis, a marked leukocytosis is present. The color index is often high, the red cells oversized, and megaloblasts abundant. As a rule, however, this type of anæmia is more apt to be associated with a chronic poisoning, such as has been produced experimentally by Bunting with ricin.

Chronic Secondary Anæmia.—In cases of moderate severity, such as those associated with malaria, syphilis, chronic nephritis, hepatic cirrhosis, etc., the blood picture is usually that described in detail in the first part of the section on posthemorrhagic anæmia; that is, we have the conditions often supposed to be peculiar to chlorosis, slight oligocytosis, more or less marked achromia, with low color index, slight or moderate poikilocytosis anisocytosis, an occasional normoblast, rarely a megaloblast, and moderate degrees of abnormal staining reaction. In cases due to infectious disease or neoplasm, a polynuclear leukocytosis may also be present.

Certain peculiarities of special types of mild, chronic secondary anæmia may be further mentioned. In *lead poisoning* we have an extraordinary prevalence of stippled, sometimes also of nucleated red corpuscles, even in the absence of any other evidences of severe anæmia. Among the nucleated red cells present, a very considerable proportion, and occasionally even a majority, may be megaloblasts. (See Plate V, Fig. 1.)

In *splenic anæmia* the color index is often lower than in any disease except chlorosis. Leukopenia is often extreme, and in several cases I have noticed an extraordinary large number of stippled erythrocytes, although the other evidences of anæmia were not striking.

In the *anæmias of infancy* there are certain well-marked deviations from the type familiar in the adult.

Causes which produce in the adult an anæmia of the mild achromic type, with small red cells and a normal leukocyte count, are apt to be accompanied in the infant by—

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(*a*) Enlargement of the spleen.
(*b*) A more or less extensive leukocytosis.
(*c*) A high color index and a megalocytic blood picture.
(*d*) A large number of erythroblasts, among which megaloblasts are very frequent.
(*e*) The presence of abnormal leukocytes (myelocytes, stimulation forms).

All these facts make it much more difficult in infancy to recognize the type of blood disease and to make an accurate prognosis from the blood alone. Indeed, the attempt should never be made. Diagnosis and prognosis should depend upon the other features of the case, the nature of the cause and the percentage of hæmoglobin.

In *anæmias due to intestinal parasites* the blood may be absolutely identical with that of pernicious anæmia, as has been proven by Schaumann in fish tapeworm anæmia, or may be rather of the achromic, small-cell type, as in most cases of hookworm disease, with which also a marked eosinophilia is also associated. In all severe parasitic anæmias, however, diagnosis should rest not upon the blood findings, but upon the presence of the parasite or its eggs in the stools.

In *anæmia associated with cancer*, especially that with some cases of gastric cancer, the resemblance to pernicious anæmia may be very striking. Aubertin has especially insisted on this point, and has reported some very carefully studied cases in which the color index was high, the diameter of the cells large, and all the chief features of pernicious anæmia accurately reproduced. The marrow, too, in his cases, was that of pernicious anæmia. One cannot help being impressed by these cases of Aubertin's, but they must be excessively rare. The writer's experience, both with gastric cancer and with pernicious anæmia, has been very large, and no case resembling those reported by Aubertin has been seen. The large experience of the Johns Hopkins Hospital, as recorded by Osler and McCrae for cancer, and by Emerson for pernicious anæmia, coincides with the writer's own experience. The usual findings in the blood of gastric cancer are typical of the ordinary type of mild chronic secondary anæmia, which gradually increases in intensity, but remains throughout of the achromic microcytic type.

LEUKÆMIA.

Definition.—A disease characterized by enormous hyperplasia of one or more of the leukocytic elements of the hæmopoietic system, elements which also flood the peripheral and especially the internal bloodvessels.

Historical.—Virchow and Bennett were the discoverers of the disease (1841), and Ehrlich sharply distinguished its two forms (1883). Within the last five years Pappenheim has marshalled important evidence tending to unify the different types of this disease by re-asserting in a modern form Neumann's hypothesis (1874) that all cases represent essentially a disease of the marrow. This point will be discussed in the next section.

The Two Common Forms of Leukæmia, Lymphoid and Myeloid; their Points of Identity and of Difference.—According to the idea of leukæmia that held sway from 1870 to 1900, and was supported especially by Ehrlich, the disease has two forms: (*a*) The splenic myelogenous. (*b*) The lymphatic. The first was supposed to be characterized by hyperplasia of all the marrow

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elements and of the spleen, the second by hyperplasia of the lymphatic glands; in both forms the new-formed cells overflow or break into the blood in great numbers, giving rise to characteristic blood changes. That many cases correspond with this conception is still admitted to be the case, but further study of the histology of the marrow has brought out the following facts:

1. In most, if not in all, cases of "lymphatic" leukæmia the marrow is more or less completely transformed into "lymphoid" tissue, *i. e.*, into tissue substantially identical with that found in the lymphatic glands.

2. There is no reason to believe that this change is due to metastasis from the glands, or that it is secondary in any sense to the glandular changes.

3. A considerable number of cases have been reported in which, although the blood showed the changes characteristic of "lymphatic leukæmia," there was no enlargement of the lymphatic glands nor of the spleen, the changes being confined wholly to the marrow.

4. In some of these cases glandular hypertrophy appeared late in the course of the disease.

All these considerations have usually been adduced as proof that the marrow changes are always the starting point and essential feature of the disease, both in the "lymphatic" and in the "splenic myelogenous" forms of the disease. It seems, however, more reasonable to conclude (especially in view of certain other facts soon to be mentioned) that the *whole hæmopoietic system*—marrow, spleen, and lymph glands—*is involved in every case of leukæmia*, the changes preponderating sometimes in the marrow and spleen, sometimes in the glands.

In support of this view we may adduce all the facts above mentioned, facts tending to show that the marrow is more or less involved in every case of the "lymphatic" as well as of myeloid type, and also the following:

1. Careful examination of the lymph glands in cases of the "splenic myelogenous" type show that although these glands are rarely much enlarged, many of them exhibit, on histological examination, essentially the same structure which is found in the marrow.

2. The enlargement of the spleen, an organ which is, on the whole, nearer to the glands than to the marrow, although sharing some of the characteristics of each, occurs not only in the "splenic myelogenous," but also in many cases of the more chronic and some of the more acute types of "lymphatic" leukæmia.

3. There are on record a few cases of chronic "lymphatic leukæmia" in which the marrow changes were absent or very slight, and at the other extreme some cases of "splenic myelogenous" leukæmia show very slight degrees of myeloid transformation in the glands.

The result of these considerations seems to be this: The leukocytic hyperplasia, which in all cases of leukæmia is the essential change in the hæmopoietic system, may begin in any part of that system, in the glands, in the marrow, perhaps in the spleen, just as amyloid or fatty metamorphoses may begin in any part of the liver. Yet we do not on this account say that the disease in one part *caused* the disease in another. It *sprang up* first here, later there—that is all. So in hæmopoietic tissue, although separated in many nooks and corners of the body, in bone and spleen, in definite macroscopic lymph glands, and in the interstices of other organs, wherever the lymphatics extend, a hyperplasia may spring up. If it grows slowly it remains more or less localized at its starting point and the symptoms are mild,

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as in "chronic lymphatic leukæmia." If it chances to start in the marrow and to be of the "lymphoid" type, it runs a quicker course and may kill the patient before it has had time to get under way in the spleen and glands. If it lasts long, all the hæmopoietic tissues will be more or less involved. Probably the disease is never strictly local and never as widespread as it might be. It is a matter of degree.

That the hæmopoietic system is essentially one and not sharply differentiated into lymphoid and myeloid elements is the postulate of the above conception of the leukæmic process. This same postulate of the *underlying unity* of these spatially separate and morphologically differentiated parts (marrow, spleen, and glands) makes intelligible the "myeloid" transformation of glands in the "splenic myelogenous" cases and the lymphoid transformation of the marrow, in the "lymphatic" cases.

Hæmopoietic tissue in embryonic life is far less differentiated. Red-cell formation is not confined to the marrow but is shared by the liver, spleen, and by some at least of the lymph glands. Indeed, in some of the lymph glands, especially in those along the vertebral column, red-cell formation appears to last on into adult life. The specialization is considerable, but not complete. Again, there can be no doubt that the marrow is concerned in the production of almost every type of leukocyte found in the blood, and although it is doubtful whether any considerable small number of small lymphocytes are normally formed there in the healthy adult, there is no doubt that it is very prone to revert to a "lymphoid" type of cell formation when thrown out of its normal working by diseases of various kinds (smallpox, typhoid, whooping-cough, pernicious anæmia, as well as leukæmia).

Reversion to a less specialized type of cell formation results, if the marrow type prevails, in bringing the spleen and glands into line, *i. e.*, in general myeloid transformation more or less widespread. If the lymphoid type prevails the marrow is brought into line with the lymph glands. In either case *differences tend to disappear, identities to be accentuated*, sometimes one, sometimes another part of the hæmopoietic system prevailing over the rest.

This explanation is more in harmony with the facts than any theory of a metastasis or transplantation of marrow cells into the glands or of gland cells into the marrow.

Some of the problems in the pathology of the disease, *e. g.*, its relation to the neoplasms, the infections, and the anæmias, will be considered later.

Despite the essential and fundamental identity of all forms of leukæmia, the cases divide themselves conveniently into three groups differing in important chemical and hæmatological details:

1. Myeloid leukæmia.
2. Lymphoid leukæmia.
3. Atypical leukæmia.

Myeloid Leukæmia.—Etiology.—The disease is a rare one, fully five times as rare as pernicious anæmia and about as rare as myxœdema. Practically nothing is known as to its cause. It certainly has no known relation to inheritance, to the climacteric, to previous hemorrhages, to malaria, or to injury. It is nearly twice as common in males as in females. Of our 87 cases, 54 were in males and 33 in females. The disease occurs most often between the thirtieth and the fiftieth year; thus of 89 cases in this series, 53 occurred between thirty-one and fifty. After sixty it is distinctly rare, only 1 case

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of this series being beyond that age. Before the twentieth year it is uncommon, distinctly more uncommon than the lymphatic form of the disease. There were 17 cases of this series between twenty-one and thirty years of age, only 9 before the twentieth year. It is a fact of some interest that among the cases occurring in young persons the female sex predominates, as it does in pernicious anæmia, although in the whole series as above noted the males were very much more numerous.

There is no reason to believe that the disease has any special relation to race, season of the year, occupation, or place of residence. Although the possibility has been often suggested that the disease is due to an infection, there is as yet no definite evidence that this is true, and the weight of probable reasoning inclines us against this hypothesis and in favor of a close relationship to the neoplasms.

Pathology.—There are no important lesions other than those of the blood-making organs. Hyperplasia of the leukocytic elements of the bone-marrow with myeloid transformation of the spleen and of the whole lymphatic system to a lesser extent, intracapillary myeloid infiltration (intense and widespreading in the liver, less marked in the lungs), such are the essential lesions of the disease.

The Spleen.—Myeloid transformation of the organ goes on unchecked in most cases, obedient to that mysterious stimulus which calls the whole blood-making system into unnatural activity, and since the spleen is not hindered (as the bone-marrow is), by definite limitations, it may grow larger and larger almost to the time of death. Spleens weighing 4000 to 5000 and even 7000 grams are on record. Despite the enormous increase in its size, the spleen usually preserves quite faithfully its normal shape. Its surface is usually smooth, hard, and coated or mottled with gray or grayish white areas of fibrous tissue, due to that perisplenitis which is almost always present to some degree, usually binding the organ firmly to the diaphragm and abdominal walls or to adjacent organs.

The gross appearances of the section surface depend largely upon the amount of fibrous tissue present. If sclerosis is extensive, the organ is converted into a tough, grayish mass which creaks under the knife. Where there is but little fibrous tissue the organ has a grayish-red tint more or less mottled with lighter gray and darker red areas. The consistency of spleens of this type are much softer than the fibrous type, although usually somewhat harder than the normal spleen. Areas of hemorrhage or infarction are sometimes present.

Microscopic Appearances.—The organ is converted into a tissue so closely resembling the marrow that the two might be easily mistaken for each other. The Malpighian follicles are practically gone; their place is taken by masses of leukocytes packed together with scarcely any recognizable connective tissue intervening, but channelled here and there by capillaries and sinuses recognizable by their lining of definite endothelium and by the larger number of red cells which they contain when compared with the surrounding tissues. Among the cells which make up the great mass of the organ we find most frequently myelocytes, then polynuclear leukocytes and transitional neutrophiles, and lastly the other granular varieties. Much less common are the non-granular mononuclear cells. A number of nucleated red cells, somewhat greater than those seen in the circulating blood, is usually to be found in the spleen. Almost the only other cell to be seen

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is the megacaryocyte of the marrow, which is fairly common and usually contains cellular inclusions. The amount of pigment and cellular debris seen in a healthy spleen is conspicuously diminished.

In cases in which the amount of stroma is increased we see the bands running especially along the sinuses and capillaries. In these cases, which usually represent more advanced stages of the disease after grave anæmia has developed, a considerable number of macrophages is found. The cells are crammed with masses of iron-containing pigment, which sometimes hides the nucleus. These cells also contain leukocytes and fragments of nuclei.

The type of disease just described represents the combination of three processes: (*a*) myeloid infiltration, (*b*) hæmolysis, and (*c*) sclerosis. The development of the latter element may be so great that it overshadows all the others, as is not infrequently the case when the disease has existed for several years. We then find that the organ has become much lighter, sometimes only one-third the average weight of the leukæmic spleens. The cellular elements are reduced to one-third or one-fifth of their ordinary bulk. The changes are identical with those above described, but the number of bands of connective tissue passing about the capillaries and sinuses becomes greatly increased. This sclerosis limits the amount of myeloid change, and thus by checking the disease process prolongs the life of the patient. It seems reasonable to explain the sclerosis as an attempt on the body's part to combat the disease or at any rate to limit its progress.

The Bone-marrow.—The bony tissues are practically unchanged; the most striking change is the banishment of fat and its replacement by a grayish-white, tough cylinder of tissue which can sometimes be turned out without breaking. After exposure to the air it takes on a redder tint, and in the ribs it is always redder than in the long bones. The changes are for the most part similar to those just described in the spleen, but in addition to these the number of megacaryocytes and their size is greater than in the spleen. We find a much larger number of non-granular mononuclear cells (undifferentiated? primordial?), although these cells are less numerous than in the marrow of many cases of infectious diseases or of pernicious anæmia. Very many of the myelocytes are in process of division. Nucleated red cells are plentiful, although much less numerous than in pernicious anæmia. The number of fully developed red cells is small and contained mostly within the sinuses. There are relatively few macrophages and slight evidences of hæmolysis.

Lymphatic Glands.—Rarely is any gross enlargement to be found in the peripheral groups. The intra-abdominal glands are found slightly enlarged, and sometimes attain the size of a walnut. Microscopic examination shows that some of the glands are perfectly normal, others partly transformed into myeloid tissue, while others are almost entirely myeloid in character. The number of megacaryocytes is larger than that found in the spleen and distinctly comparable to the number seen in the marrow. Evidences of leukolysis are abundant, but there is only a little iron pigment or other evidences of erythrolysis. Occasionally there is some myeloid change demonstrable in the tonsils, Peyer's patches, the intestinal follicles, and in the connective tissue of the omentum.

The Liver.—Great enlargement is the rule; the organ often weighs from 5000 to 6000 grams. It is grayish yellow in color, homogeneous, and without

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much indication of the normal markings. The essential histological change is a stuffing of the capillaries with leukocytes similar to those in the spleen and marrow. The crowding is so great that the normal liver cells, pushed to the wall, atrophy and disappear in large numbers. There is little if any infiltration outside of the capillaries, and the areas, which appear at first like solid leukæmic tumors, are in fact bunches of capillaries which have coalesced after the disappearance of the liver cells driven out of existence between them. Within the capillaries the number of red cells is much smaller than in the peripheral vessels. Considerable amounts of iron pigments are to be found, especially in long-standing, anæmic cases. The great size of the liver is to be explained by its unusual richness in capillaries and by the fact that the blood laden with leukocytes coming from the spleen goes first and directly to the liver.

The Lungs.—Since the blood after leaving the spleen and the liver goes straight to the lungs, it is natural that the greatest myeloid infiltration (after that in the organs just mentioned) should occur in the lungs. The conditions are practically the same as those just described in the liver, although much less in degree. Here, as in the liver, the capillaries seem to contain far more white than red cells. The air spaces are encroached upon by the distended capillaries, and the circulation through the lung is thus much impeded.

Symptoms.—*Mode of Onset.*—The patient usually seeks medical advice because he has noticed on the left side of the abdomen *an enlargement, which is in fact the spleen.* In 32 (or over one-half) of the 61 cases, splenic pain with enlargement or splenic enlargement without pain, brought the patient to his physician. A simple enlargement without pain is twice as common as enlargement with pain (22 cases to 10 cases). About one-third (21 out of 61) of the patients are first made aware of their illness by a *loss of weight and strength.* In 5 cases of the series *fever or chill* was the first symptom, while in 3 cases the disease was ushered in by *diarrhœa.*

Later Symptoms.—For many months the patient may experience no further discomfort. In most cases there is a gradual loss of flesh and a certain amount of inconvenience from the weight of the growing spleen, which drags upon the ligaments and stretches the adhesions which join it to the diaphragm, the abdominal walls, and the surrounding organs. Yet many patients feel perfectly well, and no doubt there is in most cases a long latent period during which the patient is actively at work, although the disease is steadily progressing. We get the impression certainly that most of our cases have existed for months or even years before the patient consults a physician. A few rare cases are on record in which hemorrhage, even fatal, has been the first sign of the disease, but, as a rule, such *hemorrhages* as occur are moderate in degree and come later in the course of the disease. Out of 66 cases with good notes upon this point, 52 showed *hemorrhage* at one or another period of the disease. Nose-bleed is the commonest form of bleeding, and occurred in 17 of the series. Retinal hemorrhage was found in 7 cases, bleeding from the bowels in 6 cases, and bleeding from the gums in 5 cases. Blood appeared in the urine in 5 cases, and under the skin in 4 cases. There was uterine hemorrhage in 3 cases, gastric hemorrhage in 2 cases, pulmonary hemorrhage in 1, while in 1 case sudden death occurred from cerebral hemorrhage in a patient previously in good health. Yet despite the fact that five-sixths of the cases show *hemorrhage* at some time, it *is rarely a prominent symptom* in the course of the disease.

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Rapid loss of weight occurred in practically every case of the series, although the patients did not often complain severely of it.

Gastro-intestinal disturbances are troublesome only in the latter stages of the disease when marked anæmia has supervened. Only 10 of the patients were altogether free from gastro-intestinal symptoms. Yet, as a rule, they did not cause much suffering. Nausea and vomiting were noticed in 32 cases, lack of appetite in 13, diarrhœa in 34, constipation in 22, and flatulence in 9. Occasionally the diarrhœa is early and obstinate.

Respiratory symptoms are limited almost entirely to *dyspnœa*, which is presumably to be explained by the leukocytic overcrowding of the pulmonary capillaries and a consequent encroachment upon the breathing space. As to the result of this, there is usually some pulmonary œdema in the latter part of the disease, and not infrequently an *effusion* occurs *in one or both pleuræ*, especially in the left—a localization for which the proximity of the spleen is probably responsible. As a result of the pulmonary œdema or pleural effusion most patients are troubled more or less in the latter part of the disease by *cough*, but it is not at all a prominent symptom.

In a few patients much distress is caused by *deafness* due to a leukæmic infiltration of the labyrinth. Deafness (presumably of this type) occurred in 6 cases of this series. Difficulty of vision is seldom complained of (only in 6 cases of this series), although retinal hemorrhage is relatively common.

Priapism due to leukæmic infiltration or thrombosis of the corpora cavernosa has been repeatedly mentioned in literature, but, strangely enough, did not occur in any of the 89 cases of this series.

Owing to the great increase of the excretion of uric acid, presently to be referred to, now and then a patient suffers from gravel or from stone in the kidney.

The nervous system shows practically nothing, although the occasional occurrence of facial paralysis or of neuroretinitis has been noted.

Fever was present at some time in practically every case (88 out of 89) in this present series. As a rule it ranges under 102°, and persists for a few weeks at a time in the more advanced and anæmic stages of the disease, but in 28 cases of this series the temperature reached above 102° and in 6 above 104°.

Anæmia.—In the early stages of the great majority of cases there is little or no anæmia and the patient has no symptoms referable to it, but before the fatal termination of the disease in at least two-thirds of all cases anæmia causes considerable suffering. The symptoms are those ordinarily noted in anæmia from other causes, namely, muscular weakness, shortness of breath, gastro-intestinal disturbances, œdema, headache, vertigo, and attacks of faintness.

Physical Examination.—In early cases the most striking feature is the *enlargement of the spleen*, which is usually very considerable even when the patient first consults his physician. In 85 out of our 89 cases the spleen reached the level of the navel or lower. In 3 cases it is noted as "palpable" only; in one case it reached only two fingers below the margin of the ribs. In 13 cases it reached to or slightly below the level of the navel. In about one-half of the cases (32) it extended to the crest of the ilium, and in a slightly larger number (37) it extended to the pubes. These figures represent the state of things as ordinarily found and usually described in literature. The surface of the organ is ordinarily smooth and hard; it was so in nearly

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every case of the present series. On the upper or median edge one or more deep notches are usually to be felt. One distinguishes the organ as the spleen and nothing else, largely by its shape, which, despite its great enlargement, is strikingly well preserved. Its flattened shape and sharp edge contrasts, as a rule, with the rounded, shelving, edgeless contour of tumors arising from the kidney. Inflation of the colon further serves to distinguish a kidney tumor from an enlargement of the spleen, since by this procedure the spleen is forced forward close beneath the abdominal wall, while the kidney is forced back and a tympanitic resonance may then be obtained in front of it.

The splenic enlargement may go on progressively until the death of the patient, but if an overgrowth of fibrous tissue occurs in it, the increase in size may be checked, simultaneously with a check in the increase in the number of white corpuscles. The organ may then become smaller, especially in the most chronic cases, but still, as a rule, it preserves its characteristic shape and smoothness of surface. Sudden enlargement of the spleen may be the result of hemorrhage into its substance, while sudden diminution in its size may follow infectious disease occurring as a complication, or may result from an attack of diarrhœa. Such diminution in size of the spleen also occurred in the periods of general improvement, whether these occurred spontaneously or as a result of infectious disease or *x*-ray treatment. Rupture of the spleen with immediate death occasionally occurs, as in the case recently reported by Joseph L. Miller.

The liver is almost invariably enlarged; only in 3 out of 58 cases of this series was no enlargement found. In the majority of cases in this series it extended from one to four fingers' breadth below the ribs, but in 16 cases (or slightly more than one-quarter) it reached the level of the navel and in 4 cases it extended from one to three fingers' breadth below this point.

The superficial lymphatic glands are very often as palpable as they are in health, but rarely are they considerably enlarged. Thus, in this series, out of 61 cases carefully examined with reference to this point, 10 showed no glandular enlargement, 45 showed only such slight enlargement as is frequently found in healthy persons, and only 6, or less than 10 per cent., showed marked increase in size. The glands are felt with about equal frequency in the neck, the axillæ, and the groins, but we practically never find those huge masses so often seen in Hodgkin's disease.

Eyes.—In 2 cases of this series a unilateral exophthalmos was seen, presumably due to leukæmic infiltration or hemorrhage into the orbit. Optic neuritis was seen in 2 cases, œdema of the disk in 1 case, and retinal hemorrhage in 7 cases out of 17 examined in the early stages of the disease.

Urine.—The most striking and important feature is the great excess of uric acid due to the breaking down of nuclei from the death of white cells. In no other disease is so great an increase of uric acid regularly found, and it is an interesting fact that most of the symptoms often attributed to an excess of uric acid in the system are not found in leukæmia. The occasional occurrence of renal stone or gravel has already been alluded to. Gouty manifestations do not occur, so far as known to the writer. Aside from this change there is nothing of importance. In 26 out of 56 cases in this series (or about 50 per cent.) albumin without casts was found, and in 16 other cases albumin with casts appeared. In other words, 75 per cent. of the cases showed albumin or casts, or both. Only in 12 cases (or 20 per cent.) was the absence of both of these abnormalities definitely established.

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Blood.—The enormous increase in the white cells, whence the disease derives its name, is naturally the first point of interest. As a rule, the case is "full blown" from the start; that is when the patient first comes to us the myeloid hyperplasia, and the resulting enormous increase in the number of circulating leukocytes, is already established. In fact, there is but one case on record so far (that of Charles E. Simon) in which the onset of the disease has been observed. In 71 cases with careful records, the average number of white cells was about 410,000 per cmm., at the time when the patient first felt sick enough to consult a physician. Most cases range between 100,000 and 500,000. In 46 of the series the count fell within these figures, yet higher counts are not unusual; 13 cases ranged about 700,000 and 5 reached above 1,000,000. In these 5 cases the actual counts showed respectively 1,554,000, 1,493,000, 1,328,000, 1,072,000, and 1,046,000 cells per cmm. At the other extreme are 5 cases in which the count reached only from 60,000 to 100,000.

The patient's symptoms and the gravity of the disease are not accurately measured by the degree of increase of white cells. Some patients with a relatively low count feel much worse than others with a much higher count, yet in a general way it may be stated that the higher the count the worse the patient feels, and that in most, although not in all, cases a fall in the count is accompanied by an improvement in all the other symptoms.

The increase of white cells is made up chiefly of the ordinary varieties seen in normal blood. The abnormal cells, chiefly *myelocytes*, range usually between 30 and 50 per cent. It is rare to find more than 50 per cent. (6 cases out of 53 of this series), and not at all infrequently the myelocytes fall below 30 or even below 20 per cent. (See Plate VI, Fig. 1, M.)

About equal in number, or slightly more numerous, are the *polynuclear neutrophilic leukocytes*, which in 70 per cent. of the series made up between 30 and 60 per cent. of all the leukocytes present. It should be realized that this means an enormous absolute increase in the number of these cells in the circulating blood. We are apt to think of the blood in leukæmia as if its abnormal richness in white cells was owing chiefly to the presence of myelocytes, but, as a matter of fact, the percentage of polynuclears is usually larger and their absolute increase over their normal number is enormous—not less than forty-fold. In 8 cases of this series the polynuclear cells were relatively as well as absolutely increased; in 3 cases they ranged between 70 and 80 per cent. Rarely (only 8 cases of this series) do they fall below 30 per cent. All these percentages of polynuclear neutrophiles would probably be increased if we did not make the attempt to distinguish what are called "*transitional neutrophiles*," forms intermediate between the myelocytes and the polynuclear cells and usually making up at least 7 per cent., often more, in our differential counts. (See Plate VI, Fig. 1, TN.)

Another point on which special emphasis should be placed is the increase in the actual number of *lymphocytes*, including both the smaller and larger varieties. While it is true that small lymphocytes are occasionally absent, or very scanty (as in 6 cases out of 50 in the present series), they are usually present (from 1 to 5 per cent.), and these percentages when reduced to the absolute number of cells per cubic millimeter represent a considerable increase over the number of lymphocytes in the normal blood. What has just been said of the small lymphocytes applies with more force to the larger forms, the non-granular mononuclear leukocytes, to which so many different

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names have been given. Of these forms between 3 and 30 per cent. are usually present. In only 16 of the cases did they fall below 3 per cent., while in 2 cases they rose (near the time of death) above 30 per cent. They are of special significance in relation to the problem of the two forms of leukæmia and their relation to each other. (See Plate VI, Fig. 1, L.)

Mast cells are almost always greatly increased. In two-thirds of the cases of this series they ranged above 3 per cent., and in one-third of the cases above 5 per cent. Twenty per cent. is the highest observed by the writer, although others have noted much larger numbers. (See Plate VI, Fig. 1, M A.)

The number of *eosinophiles* is almost always increased if we fix our mind upon absolute numbers and not upon percentages. The misunderstanding of Ehrlich's original dictum upon this point has now apparently been removed, as we have come to comprehend that he was speaking of actual numbers and not of percentages. Even in percentages fully one-half of our cases ranged above the normal. A small percentage of the eosinophiles, usually between 0.5 and 5 per cent., are mononuclear, and have received the name of *eosinophilic myelocytes*. Their presence is not peculiar to this disease, although they are rarely seen in such numbers in any other.

The cells of the different types above referred to vary more or less from their normal morphology in most cases of leukæmia; the polynuclear cells are often much undersized, less often gigantic. The number of granules which they contain is sometimes very much reduced, and occasionally no granules at all can be made out. This is usually in the severest cases or near the fatal termination. In the lymphocytes the number of "azur" granules is often considerably greater than the normal, and is sometimes so great that we find it difficult to distinguish these cells from ordinary myelocytes, especially as the granules exhibit every gradation in tint from the brightest crimson to the darkest blue. The occurrence of considerable numbers of supposedly "primordial" cells has already been referred to above. In the eosinophiles we find the same abnormal types already referred to in the neutrophiles, viz., dwarf cells, giant cells, and abnormal scantiness of granules. Occasionally, also, there are present in the same cell granules which, judging from their color and size, appear to belong to very different types.

Red Cells.—The fact that *anæmia is a relatively late complication* and not an early or necessary symptom of the disease has been mentioned. In 5 cases of the present series the number of red cells was practically normal when the patient first came under observation, and in almost one-half of the cases the anæmia was slight or moderate (3,000,000 to 5,000,000 cells per cubic millimeter). Sooner or later, however, grave anæmia almost always supervenes, and in 36 cases out of 61 in the present series the red cells were between 2,000,000 and 3,000,000 when the patient was first seen. Even lower figures (1,000,000 to 2,000,000) are recorded in 9 cases, but all of these were late cases. On the other hand, it occasionally happens that the patient lives for years, and even approaches the end of his life, with very slight anæmia. This was true in 4 cases of the present series. When remissions occur, whether spontaneously or as the result of infectious disease or *x*-ray treatment, the patient's improvement usually runs parallel with a gain in the number of red corpuscles, and in favorable cases the anæmia may almost altogether disappear and remain absent for considerable periods.

The *color index* is usually low, as in 60 out of 69 cases of this series. In 6

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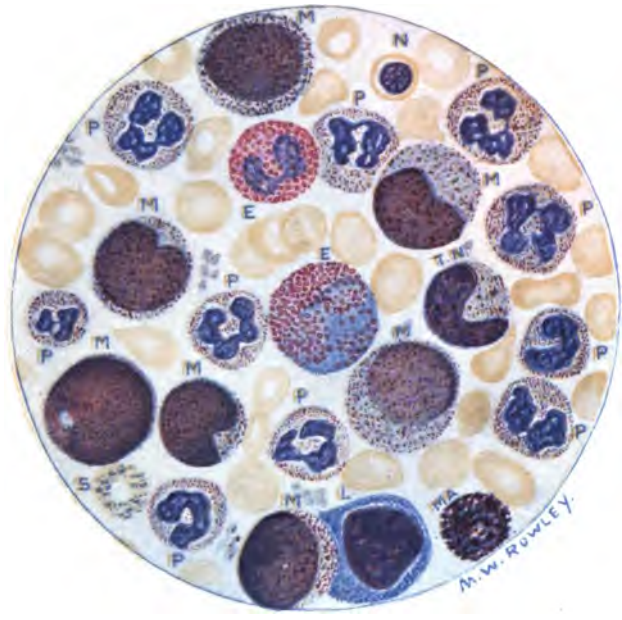
PLATE VI

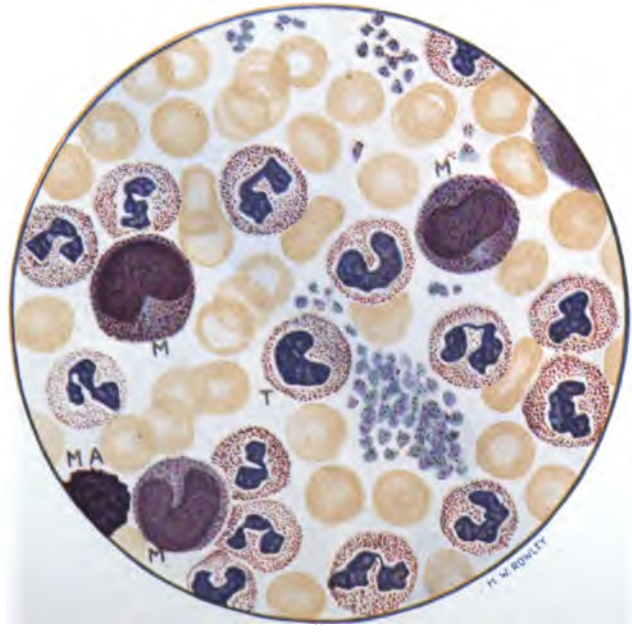
FIG. 1



Myeloid Leukæmia.

Copied from an actual field: *P*, polynuclear neutrophilic leukocytes; *M*, neutrophilic myelocytes; *T N*, transitional neutrophile; *M A*, mast cell; *L*, "marrow lymphocyte;" *E E*, polynuclear eosinophiles; *S*, "stippled" erythrocyte; *N*, normoblast.

FIG. 2



Myeloid Leukæmia after X-ray Treatment.

Fourteen typical polynuclear neutrophiles; *M*, rather atypical myelocytes; *M A*, mast cell; *T*, transitional neutrophile. Excess of blood platelets.

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cases it was high and in 3 normal. In other words, the type of anæmia usually corresponds, in this respect as in most others, to the ordinary secondary or symptomatic type. The individual red cells are usually small, pale, and moderately deformed, the degree of these changes depending upon the severity of the anæmia.

Nucleated red cells are invariably present, *even in the absence of anæmia.* Indeed, they may be as numerous in the cases without anæmia as in anæmic cases. As a rule, both the larger and the smaller varieties are present. Thus, in all the 47 cases of this series, in which special attention was paid to this point, normoblasts were present, and in all but 4 of these same cases megaloblasts were also present. In two-thirds of the cases (24 out of 34) the normoblasts were in excess, while in 10 cases the megaloblasts predominated.

In practically every case the number of blood plates is greatly increased.

Differential Diagnosis.—Few diseases are so easy to recognize. The presence of an enlarged spleen, suggested by the patient and verified by the physician, leads to a blood examination, and thus in 99 per cent. of cases to a rapid and accurate diagnosis. Only gross negligence or ignorance can lead us astray. The writer twice found sarcoma of the left kidney with enormous polynuclear leukocytosis in patients previously supposed to have leukæmia, but the blood and the tumor were both utterly unlike leukæmia. Twice he has seen a surgeon cut down on a leukæmic liver, but only because he was bound to make his diagnosis by operating, and disregarded the obvious facts which blood examination had previously revealed. During the stage of remission, when the blood has returned to normal, diagnosis may be impossible, but the history usually prevents mistakes.

A number of rare atypical forms of the disease will be discussed later. Some of them present difficulties—even insuperable ones—in classification *intra vitam,* but as such are very rare and almost invariably run the same course as ordinary leukæmia (acute or chronic), their precise title is not of any great importance.

Course, Duration, and Prognosis.—Almost invariably the disease pursues a chronic course. In the whole literature not more than a dozen cases are on record in which the symptoms may be properly called acute. In this series only 10 out of 84 cases lasted less than six months, even if we accept at its face value the patient's statement as to the duration of his disease before he consulted his physician. Most cases last from one to three years (42 out of 84 in the present series); 14 of the cases lasted more than three years, and 28 less than one year. Very frequently the disease remains latent, that is to say, produces no considerable discomfort for many months, and although the patient is aware that he has an enlarged spleen he does not consult a physician. But at any time in the course of this apparently latent disease an acute, even fatal, aggravation may take place, and in carelessly recorded cases these acute terminations of chronic cases are first spoken of as "acute cases."

In an uncertain but probably rather small percentage of cases spontaneous remissions occur and both blood, spleen, and all the other tissues may return, so far as we know, to the normal. The same thing may occur as a result of any of the infectious diseases presently to be mentioned as complications. Sometimes such remission occurs during the administration of arsenic, possibly as its result. There is no doubt, however, that as a result of

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x-ray treatment a great improvement does occur in most cases. There is no possibility any longer that this improvement should be looked upon as a coincidence, yet, so far as we can say, up to the present time true recovery is unknown.

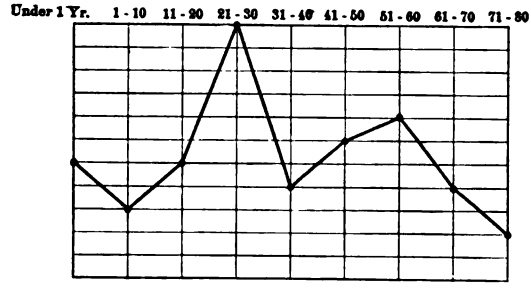
Complications.—Infection by pyogenic organisms occurred in 15 cases of the present series. Among these 15 cases there were 3 of erysipelas, 2 of carbuncle, 3 of terminal streptococcus sepsis and various local abscesses. Next to the pyogenic infections, tuberculosis is probably the most common complication. The miliary form is most often seen, but ordinary chronic pulmonary tuberculosis also occurs. Pneumonia not infrequently occurs, and like other infections may bring about a temporary amelioration in all the symptoms. The same is true of such complications as acute articular rheumatism, influenza, and typhoid. As a rule these complications produce a rapid fall in the number of white cells. Sometimes this fall is accompanied by an improvement in all the symptoms, but sometimes these go on unchecked. Occasionally the blood count is not affected or rises still higher than during the occurrence of the complication.

Lymphoid Leukæmia.—Conditions of Occurrence.—Nothing of importance is known as to the cause of the disease. It is distinctly more rare than myeloid leukæmia. Thus in the last twelve years the writer has seen 89 cases of myeloid leukæmia and in the same period only 51 cases of lymphoid leukæmia. Both forms are from five to ten times rarer than pernicious anæmia.

Age.	Cases.	
2 to 4 months	5	25 acute cases (3 weeks to 3 months).
1 to 10 years	3	
11 to 20 years	5	
21 to 30 years	12	
31 to 40 years	4	(2 acute, 2 chronic).
41 to 50 years	6	(3 acute, 3 chronic).
51 to 60 years	7	13 chronic cases, (6 months to 4 years).
61 to 70 years	4	
71 to 80 years	2	
	48	

The irregular distribution of the cases in this table is better seen in the following form:

FIG. 59



It suggests that we are dealing with a mixture of two or more sub-types, and a closer analysis of the cases shows this to be true. One type of the

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disease—the acute form—is much more common before the thirty-first year than after it (22 cases under thirty-one, 5 cases over thirty-one years), while the *chronic* form of the disease is represented in this series *wholly* by cases occurring in persons *over* thirty-one years of age. There were 18 chronic cases, 13 of which (or nearly 80 per cent.) occurred in patients over fifty-one years of age, while not a single acute case occurred after the fifty-first year.

Sex.—There were in the series 31 males and 14 females, while in 3 of the infants the sex was not recorded. Obviously the disease is much more common in males, as is shown by the statistics of all the articles on the subject. Race, residence, occupation, season, seem to have no relation to the disease.

Symptoms.—*The onset* may be acute and stormy or gradual and insidious. Acute cases usually begin with weakness and fever; sometimes, however, there is glandular enlargement (as in most chronic cases) preceding the appearance of any other symptom. Combining both types—the acute and the chronic—we find that the following are the modes of onset:

	Cases.		
With enlargement of glands	20		
With weakness and pallor	15	21	41 cases.
With fever	6		
With abdominal pain and swelling	3	6 cases.	
With enlargement of spleen	3		
With hemorrhage	1		

In the chronic cases the *glandular enlargement* may last almost unnoticed for years, until the comment of a friend or some trifling digestive or respiratory disturbance brings the patient to a doctor. In acute cases the enlargement may be rapid, but in the most acute of all there is often no enlargement externally, the disease being confined to the marrow and internal glands or wholly to the marrow.

Weakness and dyspnœa on exertion are present (*a*) in the cases with fever, and (*b*) in the cases with anæmia; that is, chiefly in the acute cases or in late stages of any case. The evidences of anæmia appear, as a rule, earlier than in the myeloid form of the disease. Thus in 34 cases the writer found marked anæmia at the first examination of 30, or nearly 90 per cent., while only 4 cases were recognized some months or years before there was any anæmia.

The *anæmia* manifests itself by pallor, mental and muscular weakness, dyspepsia and constipation, dyspnœa and œdema of the feet, headache, vertigo, and tinnitus. The degree of anæmia was marked in 34 cases, moderate in 1 case, and slight or absent in 10 cases.

Gastro-intestinal troubles are, on the whole, slight. Short periods of nausea and vomiting were present in 15, or about one-third of the cases, many of them febrile ones. Anorexia was complained of by only 11, dyspepsia by 7, constipation by only 14, and diarrhœa by 7. There is nothing characteristic about the symptoms of this group.

The *cardiac and respiratory* symptoms are simply those seen in all anæmias. In the chronic non-anæmic cases they are absent. Occasionally a pressure cough, due to enlarged bronchial glands, gives much suffering.

Hemorrhages are considerably more common than in myeloid leukæmia, but are confined chiefly to the acute cases. Among 34 cases examined with

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reference to this point there were subcutaneous hemorrhages in 17 cases, hemorrhage from the gums in 15 cases, blood in the urine in 8 cases, blood in the vomitus in 3 cases, blood in the fæces in 3 cases, and blood in the sputum in 4 cases. *Retinal hemorrhages* were found in 8 out of the 9 cases examined.

Physical Examination.—Many cases are first discovered in the course of a routine physical examination undertaken without any suspicion as to the nature of the disease. *Glandular enlargement* is the most striking feature. As a rule, the glands of the neck, axillæ, and groins are all affected (44 out of 46 cases), the kernels averaging from 0.5 to 2 cm. in diameter. They are discrete or loosely joined in small groups, usually hard, rarely tender, and movable under the skin. There are never seen any such large masses as are the rule in Hodgkin's disease. They rarely attract the notice of the passer-by and seldom give rise to pressure symptoms. The relative frequency of involvement is shown by the following figures: glands in the groins, 44 cases; glands in the axillæ, 43 cases; glands in the neck, 41 cases; tonsils enlarged, 7 cases; epitrochlears enlarged, 4 cases; and the abdominal glands palpable in 2 cases.

Splenic enlargement, although much less marked, on the whole, than in myeloid leukæmia, is present in almost every case. In 34 out of 41 cases in the series the organ was easily felt, and in several of the other cases (seen but once) it was doubtless palpable at subsequent examinations. The dimensions of the organ are shown in the following table:

	Cases.	
Spleen reached the pubes in	1	12 cases showed much enlargement.
Spleen reached below the navel, half-way to the pubes in	5	
Spleen reached the navel in	6	
Spleen three fingers' breadth below the ribs in	7	11 showed moderate enlargement.
Spleen two fingers' breadth below the ribs in	4	
Spleen one finger's breadth below the ribs in	6	13 showed slight enlargement.
Spleen "palpable" in	7	
Spleen not palpable in	5	

The characteristics of the organ are essentially those already described under myeloid leukæmia.

The liver is less often demonstrably increased in size; the notes of 34 cases showed the following:

	Cases.
Reached one finger below the costal margin in	4
Reached two fingers below the costal margin in	6
Reached three fingers below the costal margin in	7
Reached four fingers below the costal margin in	4
Reached the navel in	3
Reached two fingers below the navel in	1
	25
Liver not demonstrably enlarged in	9
	34

Loss of weight is usually marked in acute cases and slight in chronic cases. *Fever* was present in all but 5 of the cases examined. It is sometimes high and continued, so that the diagnosis of typhoid fever is considered or even made, as in 3 of the present series. More often it is irregular and

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occurs in short periods of five to ten days each. In this series the temperature reached 100° in 4 cases, 100° to 102° in 10 cases, 102° to 104° in 8 cases, and 104° or higher in 9 cases.

Ocular symptoms are rarely marked. The retinal hemorrhages above mentioned interfered with vision in only 2 cases of the series. As a rule they do not harm. Exophthalmos (unilateral) was present in 1 case; presumably it was referable to leukæmic infiltration or hemorrhage in the orbit. *Deafness* (due presumably to leukæmic labyrinthitis) occurred in 4 cases.

The urine was normal in only 7 out of 30 cases. In 7 cases it contained albumin, and in 16 albumin with casts, mostly of the hyaline and granular varieties. Blood in the urine was seen in 8 cases, and in some of these it was also adherent to casts. The increase of uric acid, so marked in myeloid leukæmia, is also present in the lymphoid form of the disease, but as the number of blood leukocytes is less increased, the uric acid resulting from their death is also less increased.

The Skin.—Three types of lesion are important: (1) Ecchymoses, sometimes minute, sometimes extensive; (2) subcutaneous abscesses; and (3) leukæmic nodules. Since there are minute collections of lymphoid tissue scattered here and there over almost every square inch of the body, we need not assume any metastases to account for the cutaneous nodules which sometimes develop in enormous numbers. Some cases of this type have been diagnosed as sarcomatosis. A discussion of the relation between sarcoma and lymphoid leukæmia will be found on page 674.

The Blood.—The gross appearance of the drop is not at all striking in this or in the myeloid form of leukæmia. Its color is dependent on the degree of anæmia present, and the only suggestion of the leukæmic change is in a slightly dull and opaque quality of the usually bright and shining surface of the drop. In the attempt to spread the drop on coverslips the practised hand will sometimes get an inkling of the real condition of things, for the masses of leukocytes make the film thick, viscous, and difficult to spread. The grade of anæmia present at the first examination of 33 cases is shown in the following figures:

		Cases.
Red cells numbered	5,000,000 to 5,500,000 in	2
" "	4,000,000 to 5,000,000 in	5
" "	3,000,000 to 4,000,000 in	7
" "	2,000,000 to 3,000,000 in	9
" "	1,000,000 to 2,000,000 in	9
" "	under 1,000,000	1
Total		33

The average count is therefore about 2,800,000 at the time when the patient is first seen. In all but the most chronic cases the count of red cells falls progressively until near death, when it is about 1,600,000 on the average. In remissions the count rises rapidly. In 11 cases of this series it averaged 3,900,000 in a remission, but only 2 cases reached 5,000,000 or higher.

The reasons for this anæmia appear to be two: (1) crowding out of erythroblastic by leukoblastic tissue in the marrow (myelophthisis), and (2) hæmolysis. As the multiplication of leukocytes in the marrow reaches large proportions, the lymphoid tissue takes up more and more (*a*) of the space occupied by fat and (*b*) later of the space occupied by young red cells. The marrow can no longer replace the red cells which wear out in use, and

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still less the increasing number which vanish by hæmolysis. Hence, the red cells are slowly or rapidly worn out and anæmia results.

The *color index* is usually low in all the earlier stages of the disease before the number of red cells has become much reduced (12 cases out of 14). When the anæmia becomes grave, the color index is apt to be high (9 cases out of 13). Thus the index was low in 12 out of 14 cases when the red cells were ranging from 3,000,000 to 5,000,000, while the index was high in 9 out of 13 cases when the red cells were ranging from 500,000 to 2,000,000.

The stained specimen shows a varying amount of anæmia with more or less achromia, poikilocytosis, abnormal staining, and nucleated red cells. Normoblasts were present in 17 out of 19 cases carefully studied. Megaloblasts were present in 13 out of 15 cases carefully studied. The normoblasts were in excess in 2 cases and the megaloblasts were in excess in 7 cases.

Leukocytes.—The excess of cells in the peripheral circulation is much less than in the myeloid cases. Whereas in the myeloid cases the average count at the first examination was about 410,000 per cmm., the average in 34 lymphoid cases was 180,000. In 20 cases, or nearly two-thirds of this series, the first count was under 60,000. The following are the figures in detail:

	Cases.
Under 10,000	1
10,000 to 20,000	2
20,000 to 30,000	2
30,000 to 40,000	3
40,000 to 60,000	8
60,000 to 80,000	4
100,000 to 200,000	7
200,000 to 300,000	2
300,000 to 400,000	2
700,000 to 800,000	2
1,505,000	1
	34

As the symptoms are aggravated and the anæmia progresses toward the fatal termination, the counts are about as likely to fall as they are to rise. The average count in 17 cases studied near death was only 300,000, yet there were 9 cases, or over one-half, with counts below 80,000.

The highest counts reached in each case are tabulated below:

	Cases.
20,000 to 30,000	2
30,000 to 40,000	1
40,000 to 60,000	4
60,000 to 80,000	4
80,000 to 100,000	1
100,000 to 200,000	7
200,000 to 400,000	4
400,000 to 1,000,000	5
1,631,000	1

From the standpoint of practical diagnosis the most interesting fact in these tables is the large proportion of low and moderate counts, comparable to the leukocytosis of infectious disease and likely to be overlooked in a hasty examination. Yet it is also true that the highest count in the present series, 1,631,000, is higher than any in the myeloid group.

Differential Count.—The blood film presents the sharpest possible contrast with myeloid leukæmia. Myeloid blood shows an almost infinite

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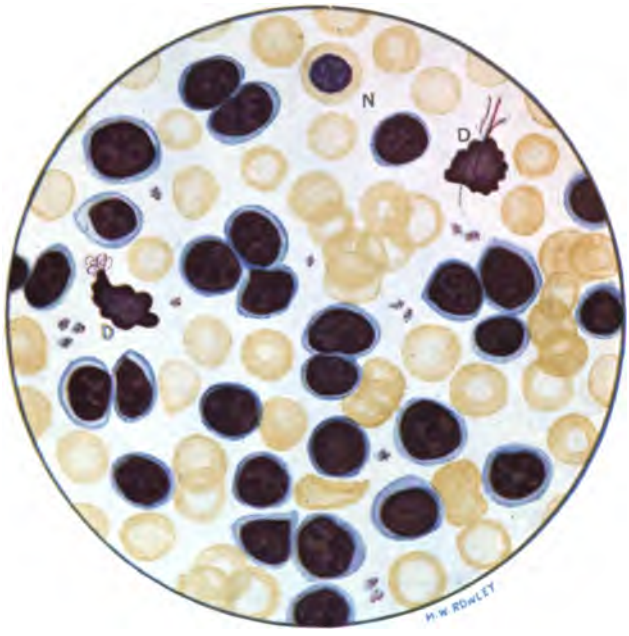
PLATE VII

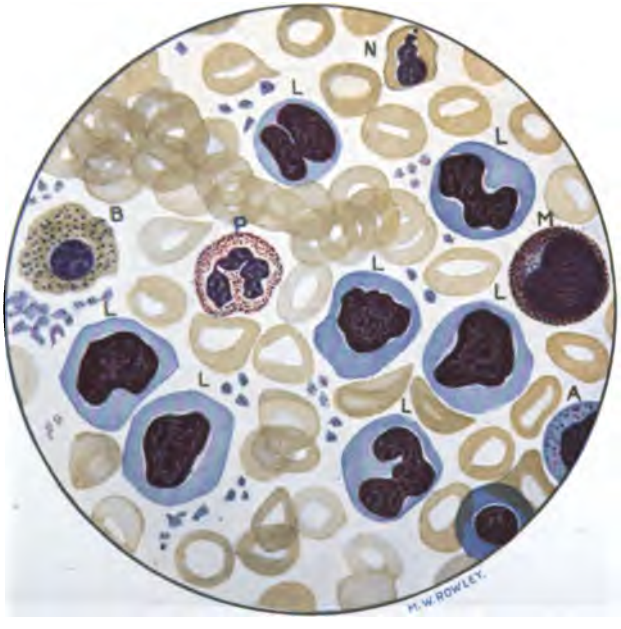
FIG. 1



Chronic Lymphoid Leukæmia. (Actual Field.)

Twenty-nine typical small lymphocytes; *D D*, degenerating lymphocytes; *N*, normoblast.

FIG. 2



Acute Lymphoid Leukæmia. (Actual Field.)

L, atypical "lymphocytes" (Naegeli's myeloblasts); *M*, neutrophilic myelocyte; *P*, polynuclear neutrophile; *A*, "large lymphocyte," with "azur" granules; *B*, megaloblast (stippled); *N*, normoblast.

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variety of cell types. Lymphoid blood shows an endless monotony—the same cells in field after field. The writer has counted 1000 cells in successive fields without finding anything but "lymphocytes."[1] In a count of 3500 cells in this case there was 99.6 per cent. of "lymphocytes." This is of course an extreme instance, but it is not at all rare to find that 95 per cent. or more of the white cells belong to a single type, and not a patient in this series had less than 60 per cent. of "lymphocytes."

	Per cent.	Cases.
"Lymphocytes" large and small)	98 to 100 in	2
" " "	95 to 98 in	8
" " "	90 to 95 in	12
" " "	80 to 90 in	5
" " "	70 to 80 in	5
" " "	60 to 70 in	1
		33

Among the "lymphocytes" in these 33 cases the large forms predominated in 14 cases and the small in 19, but in several of these it was difficult or impossible to decide in which group ("large or small") many of the cells belonged. Sometimes a large proportion of the cells were about 10 μ in diameter, *i. e.*, neither large nor small. (See Plate VII, Fig. 1.)

Thus far the prevailing cell of lymphoid blood has been referred to as a lymphocyte. In some patients, especially those running a mild chronic course, the cells have all the characteristics of the ordinary small lymphocyte of normal blood. But in many of the acute cases the prevailing cell differs distinctly from both the small and the large lymphocyte. It is difficult to tell whether the cells of lymphoid leukæmia differ from *any* of the cells known as "*large mononuclear*" in the terminology of most writers. For among the cells of this type sometimes found in the normal blood are some that correspond with the descriptions and pictures of (1) Türk's "stimulation cells," (2) Naegeli's "myeloblasts," (3) Pappenheim's "splenocytes," (4) Unna's "plasma cells," (5) Weil's "non-granular myelocytes," (6) Cornil's "markcellen," and many others. (See Plate VII, Fig. 2, L, L, L and A.)

Each of these cells fades by transitional forms: (*a*) *into each of the others, and* (*b*) *into the large lymphocyte.* Hence, all that can be said of the atypical non-granular mononuclear cells of lymphoid blood is: (1) That they belong in all probability to a group very near the primordial cells, whence both leukocytes and erythrocytes are derived. (2) That they are probably identical with some or all of the cells above catalogued. (3) That they are probably marrow cells rather than lymph-gland cells.

The Relation of the Type of Cell to the Course of the Disease (*Acute or Chronic*).—Fraenkel first called attention in 1897 to the fact that in acute leukæmia the cells were usually of the lymphoid type and usually large. He denied the occurrence of a chronic lymphatic form of the disease, and asserted that all lymphatic cases are acute and all chronic cases myeloid in type. While this statement applies to the great majority of cases of each group, there are many exceptions to it, as has been repeatedly pointed out. Cases of acute myeloid leukæmia do occur, although they are very rare. Cases of chronic lymphatic leukæmia are slightly (but only slightly) less common than cases of acute lymphatic leukæmia. In this series, 17 were

[1] The sense in which I here use this word is explained below.

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chronic (6 months to 5 years; average 2 years), 22 were acute (3 to 10 weeks; average 6 weeks), and 5 were subacute (2 to 5 months; average 3 months). The criterion in these (as in almost all the cases on record) is the duration of overt symptoms. Many classed as acute may in fact have represented acute terminal symptoms in chronic cases.

Now, in the study of the size of the "lymphocytes" in 33 of these cases, the large forms were found to predominate in 14, the small in 19; but, as said above, many cases might be transferred from the "large" to the "small" group because (*a*) there are many cases with borderline cells, neither large nor small; and (*b*) in the same case at different times the average size of the cells may vary. In a general way, however, it may be said that the large cells are rarely seen in chronic cases, while in "acute" cases either large, small, or medium-sized cells may be found. This finding accords with that of Gulland and Goodall.[1]

The *polynuclear cells* in lymphoid blood are reduced in a degree corresponding with the increase of lymphocytes. Practically all the cells are either polynuclears or lymphocytes. The *eosinophiles* and *mast cells* are, as a rule, reduced both relatively and absolutely. No eosinophiles were found in 15 out of 28 cases of this series. In 12 cases they varied from 0.1 to 3 per cent., and only in 1 case did they rise above 3 per cent. Mast cells were noted in only 2 cases. Myelocytes were wholly or nearly absent in 17 cases, under 3 per cent. in 9 cases, and between 3 and 5 per cent. in 3 cases.

The writer would interpret the presence of myelocytes in these cases (as in pernicious anæmia or ordinary leukocytosis) as a "stimulation myelocytosis," and not as a hint of a transition to mixed or myeloid leukæmia. *No mixed forms of leukæmia* have been seen in the writer's field of work.

Complications.—Tuberculosis (miliary or chronic pulmonary) is not uncommon as a complication, but the most frequent interruption of the course of the disease is one or another type of septicæmia. Thus, terminal streptococcus sepsis occurred in 5 cases, local abscess in 3 cases, toxæmic jaundice in 2 cases, and vegetative endocarditis in 1 case.

Differential Diagnosis.—Like myeloid leukæmia, the lymphoid variety is one of the easiest of all diseases to recognize, provided we do not forget to examine the blood. The only cases in which diagnostic difficulties occur are those in which no blood examination is made; such cases are especially those in which the spleen and external lymph glands present no enlargement, cases, in other words, in which the disease is confined to the bone-marrow and internal lymph glands or to the bone-marrow alone. These cases, which are usually of the acute type, will be referred to later in the section on acute leukæmia. They are apt to be mistaken for typhoid fever, tuberculosis, purpura, or septicæmia, from all of which, however, they may be readily distinguished by blood examination.

Twice in the writer's experience, however, there has risen serious doubt in the diagnosis *between lymphatic leukæmia and lymphocytosis*. The first case was one of pneumonia in a child of twelve years. The history was very incomplete and the pneumonia of the focal or bronchopneumonic type. The blood showed 94,000 white cells, 75 per cent. of which were small lymphocytes. The writer made the diagnosis of lymphatic leukæmia. Within a week the pneumonia had disappeared. Coincidently with this the blood returned

[1] *Journal of Pathology and Bacteriology*, June, 1906, London.

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to normal, and there has been since no return to the leukæmic condition. The patient is now eighteen years old. Subsequent investigation showed that the pneumonia had complicated a well-marked case of whooping-cough, and there is now no reason to doubt that the lymphocytosis was due to this cause.

Following a case of wound sepsis, acquired at autopsy, a physician of my acquaintance had a secondary lymphangitis with swelling of the glands not only on the affected side but in the other axilla. The white cells were increased to between 20,000 and 30,000, but in the differential count the lymphocytes, not the polynuclear cells, as would be expected, were in the majority, and there was serious doubt whether the diagnosis should be wound sepsis or acute lymphoid leukæmia. The course of the disease, however, was that of an ordinary case of sepsis, at the end of which the blood returned to normal, where for the past six years it has remained.

We have at present no sure method of avoiding diagnostic errors like those above referred to, but we must remember that very marked lymphocytosis occurs in most cases of whooping-cough, not only in the paroxysmal stage, but also in the complications of the disease. It must also be borne in mind that the stimuli (chemotactic?) which ordinarily produce a leukocytosis, in connection with septic lymphadenitis, may result in lymphocytosis; indeed, the wonder is that this is not always the case.

Cutaneous Lesions in Leukæmia and Pseudoleukæmia.—(1) Lymphoid tumors in the skin. (2) Various reactions of the pruriginous type (prurigo, pruritus, urticaria, eczema). (3) Generalized exfoliative dermatitis (Nicholau).

Cutaneous tumors occur almost exclusively in lymphoid leukæmia. So far there is no record of their occurrence in myeloid leukæmia, and in pseudoleukæmia they are distinctly rare. They are most common about the face, and often ulcerate. Presumably they arise, like many other leukæmic lesions, from the minute lymphoid follicles which Ribbert has shown to be scattered so thickly through all tissues. They are usually from 4 mm. to 1 or 2 cm. in diameter. Like other leukæmic and pseudoleukæmic lesions they may regress and disappear "spontaneously" or as a result of infectious disease or *x*-ray treatment. Histologically they are identical with other leukæmic infiltrations.

Sometimes, as a forerunner of leukæmic or pseudoleukæmic tumors, a variety of itching, eczema-like lesions may occur. Dry, scaling lesions resembling pityriasis—with some prurigo, but without any scar formation or retraction—may be distributed over the whole body. Its evolution is slow, afebrile, with very little infiltration. It is less erythematous than pityriasis rubra, although some authors have also described "pityriasis rubra" in pseudoleukæmia.

Features Especially Characteristic of Acute Stages of Leukæmia (Acute Leukæmia) Myeloid or Lymphoid.—Fever, hemorrhages, rapid rise (or fall) of the number of circulating leukocytes, and rapid changes in the organs affected are the most striking features. The cases are apt to be mistaken for typhoid fever, since they are associated with a high continued fever (101° to 104° or thereabouts), a "typhoidal" or drowsy mental state, enlarged spleen, and perhaps hemorrhage from the bowels. The cutaneous and buccal hemorrhages, with a spongy, ulcerating condition of the gums or tonsillar regions, recall scurvy or purpura hæmorrhagica. The drenching sweats, often accompanied by chills, or by enlargement of the liver, have led, in 3 cases known to the writer, to the diagnosis of hepatic abscess;

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malignant endocarditis or other types of septicæmia are also suggested. From all these conditions, however, the blood examination should quickly and surely distinguish the disease.

Prognosis.—Recovery, so far as is known, never occurs. Nearly half of the cases are of the acute type and die in less than ten weeks from the onset of symptoms. The chronic cases are less frequent, and may last from six months to five years. The occurrence of fever, hemorrhages, rapid enlargement, and multiplication or disappearance of glandular tumors point to an acute type of the disease. If the large forms of lymphocytes predominate in the stained specimen, the disease will probably pursue the acute course, but there are exceptions to this rule. Most chronic cases are associated with excess of small lymphocytes in the blood, but this blood picture is also seen in some of the acute cases.

In the absence of complications, the lower the leukocyte count the better the prognosis, but it should be remembered that in the presence of septicæmia or tuberculosis complicating lymphoid leukæmia, we often witness a fall in the number of white cells, synchronous with a failure of the patient's strength, so that at the time of death the leukocytes may be normal or subnormal. Other things being equal, the older the patient the better the prognosis. Remissions occur, as has already been said, sometimes spontaneously, more often following arsenical medication or intercurrent infection, and most frequently of all as a result of *x*-ray treatment. With the exception of those produced by *x*-ray treatment, remissions rarely last more than a few months. How long life may be prolonged as a result of *x*-ray therapy we cannot as yet say.

Treatment of Both Forms of Leukæmia.—Five years ago the treatment of this disease seemed practically without avail. To-day we can assure the patient in the majority of cases—that is, in practically all myeloid or chronic lymphoid cases—that very marked improvement will follow the judicious and persistent use of *x*-ray treatment. How long this improvement can be maintained we cannot as yet say. That the treatment reaches the root of the disease does not seem at all likely, but there are to-day a number of patients kept alive and in comfort for years who show as yet no signs of relapse.

The treatment should be begun as soon as the diagnosis is made, not only in early cases, with relatively mild symptoms, but also in cachectic, febrile, and emaciated patients. Some of the writer's brilliant therapeutic successes have been in cases of this type. As to the details of treatment, individual operators give different advice. The main point is to put the patient under the care of an experienced operator. Some prefer to give relatively long exposures, and to separate them by intervals of at least a week; while others treat the patient each day, or every other day, with a relatively short sitting. As to the use of hard tubes, soft tubes, deep-penetrating and superficial-acting apparatus, there is difference of opinion.

The spot selected is usually the area corresponding to the enlarged spleen, but many operators expose the epiphyses of the long bones, the liver, or the thorax in a considerable proportion of their treatments. In patients presenting marked glandular enlargements, the enlarged glands themselves should be given exposures.

Results begin to appear usually within a few weeks, and should be very marked within two months. The red corpuscles begin to increase, the number of white cells and the size of the spleen to diminish. As the white

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cells diminish in number, the differential count also rapidly changes. First, the polynuclear neutrophiles become relatively increased, as the number of myelocytes, eosinophiles and mast cells diminishes. Later, in favorable cases, the differential count may become altogether normal. The number of degenerating cells is largely increased. As the spleen diminishes in size, it becomes likewise softer and more movable. In many cases it recedes altogether out of reach behind the ribs. In glandular cases similar changes occur. The glands become more movable, more discrete, smaller, and may altogether disappear.

When treatment is intermitted, the patient may remain in good health for weeks or months. So far as known by the writer, there is as yet but one case on record with the preservation of health without treatment for more than a year. Sooner or later, the leukæmic changes begin to manifest themselves once more in the blood, and treatment must be resumed or the patient will rapidly lose ground. With the second course of exposures to the *x*-rays the patient's symptoms usually improve as before, but there is unfortunately a not inconsiderable group of cases in which treatment after relapse is unavailing. Sometimes, indeed, the *x*-rays lose power much earlier in the course of treatment; after a temporary improvement the patient begins to run down, and dies before the blood has ever reached normal and without any intermission in the treatment.

After the earlier sittings the patient may feel worse instead of relieved; his fever may rise, his lassitude increase. Sometimes these untoward effects persist as long as the treatment is used and we have to give up altogether this use of the *x*-rays. Such untoward symptoms have been attributed to an auto-intoxication due to the absorption of the products of the leukocytes disintegrated by the action of the *x*-rays. In acute cases, especially of the lymphoid type, the treatment is usually unavailing, and sometimes has seemed to hasten the fatal termination. Animal experiment shows that the *x*-rays have a selective action upon the leukoblastic tissue, and that under their use the spleen, lymph glands, and leukoblastic marrow undergo rapid atrophy.

Atypical Leukæmia.—The most important variations from the types above described are as follows:

1. *Leukæmic changes in the hæmopoietic system without leukæmic blood (pseudoleukæmia).*

2. *Leukæmic blood without leukæmic changes in the blood-making organs (circulating myelomatosis).*

3. *Apparent combinations of leukæmia with pernicious anæmia (leuk-anæmia).*

4. *Tumor-like growths of hæmopoietic tissue with or without* leukæmic blood: (*a*) Diffuse (chloroma, Sternberg's leukosarcoma); (*b*) Local (myeloma).

Less important are the supposed "mixed forms" of leukæmia and the numerous minor variations in the leukocyte formulæ (atypical blood pictures) in otherwise typical cases of leukæmia. Some of the latter deviations will be considered first.

1. **"Mixed leukæmia,"** part myeloid, part lymphoid, is certainly a great rarity, unless arbitrarily defined. In a series of 140 cases there was none which seemed to the writer to deserve such a title, and the distinction into myeloid (89 cases) and lymphoid (51 cases) was not difficult. Yet cases are often reported as "mixed leukæmia," (*a*) through pure misunderstand-

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ing of the terms ("mixed-cell" (myeloid) "leukæmia" being mistaken for "mixed leukæmia"), and (*b*) through unfamiliarity with the fact that in almost all cases of classic *myeloid* leukæmia a variable (sometimes considerable) percentage of lymphocytes is present. In some cases this percentage becomes increased (or decreased) toward the end of the disease. Yet it is improper to attribute to such trifling changes the importance implied in stating that the disease has changed from the myeloid to the lymphoid form, or *vice versa.*

Cases with high leukocyte counts and considerable percentages of neutrophiles (mononuclear and polynuclear), of eosinophiles, and of mast cells should always be classed as myeloid, even when the percentage of non-granular mononuclear forms is also large.

2. **Atypical Blood Changes in Leukæmia.**—(*a*) Absence of eosinophiles, of mast cells, or of both. (*b*) Extraordinarily high percentages of one or both of these varieties (20 to 50 per cent.). (*c*) Strikingly high percentages of polynuclear neutrophiles (70 to 90 per cent.), or remarkably low percentages. (*d*) "Plasma cell leukæmia," a condition in which a large proportion of the circulating leukocytes are regarded as plasma cells.

3. **Atypical, Sarcoma-like Growth of the Hæmopoietic Tissues.**—(*a*) The best-studied examples are those known as *chloroma.* (*b*) Attention has also been called (especially by Sternberg and by Warthin) to the fact that in ordinary non-chloromatous cases of lymphoid leukæmia, the hæmopoietic tissues occasionally invade and infiltrate organs not precisely as sarcoma does, yet in a manner suggesting it. Sternberg accordingly proposes the term "leukosarcoma" for such cases. Starting in the thymus, the tonsil, the sternum, the intestine, or elsewhere, the growths penetrate and destroy neighboring tissues, yet preserve all the while a structure indistinguishable from that of the glands and marrow of lymphoid leukæmia.

Warthin[1] reports a case in which a process essentially identical with lymphoid leukæmia (as we ordinarily recognize it in the marrow, spleen, and lymph glands) appeared to originate in the lymphatic tissue about the intestine and mesentery, which (with the stomach) were infiltrated almost from end to end with a growth composed of cells of the "large lymphocyte" type. There were metastases in the lungs, liver, kidneys, and marrow. The process also involved diffusely the spleen and marrow, but the changes were much less marked there than in the intestine. In the peripheral lymph glands no changes were found. There was no considerable anæmia, although normoblasts and megaloblasts were fairly abundant. The blood showed 97 per cent. of mononuclear, non-granular cells, most of which are described as very atypical lymphocytes.

It is obvious from the cases above mentioned, as well as from others of a similar nature, that *the leukæmic process can start wherever in the body leukoblastic tissue is present, that it may penetrate and invade other tissues,* breaking through the bones (as in chloroma), through the glandular capsules, and through the limits ordinarily preserved by the gastro-intestinal lymphatic tissue. It can give rise to "metastases," although it is doubted by some authorities whether these "metastases" are due to cells transported by the blood or lymph. If the "stimulus" which started the parent growth is exerted also upon some of the innumerable minute foci of leukoblastic tissue

[1] *Transactions of the Association of American Physicians,* 1904, p. 421.

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scattered through every organ and tissue of the body, foci indistinguishable from "metastases" may arise. It is notable, however, that the leukæmic (or leukoblastic) infiltrations and metastases do not give rise to the ordinary amount of reaction in the tissues which they invade.

Shall we say that we are dealing with malignant tumors in cases like the above? If so, shall we say that all leukæmia is neoplastic? I think we must conclude that *there are transitions from ordinary sarcoma through Sternberg's leukosarcoma and through myeloma to leukæmia of the ordinary type.*

4. **Leukæmic Blood without Leukæmic Changes in the Blood-making Organs.**—(*a*) One of the most remarkable cases of this type is that reported by Simon.[1] Following a crush of the leg with multiple fractures, the patient's blood was found to present the picture of myeloid leukæmia. With recovery of the leg the blood became and remained normal. (*b*) Symptomatic leukæmia in ordinary sarcoma (cutaneous, glandular, etc.) with normal bone-marrow has been reported. (*c*) The enormous circulating lymphocytosis of whooping-cough may render the blood indistinguishable from that of lymphatic leukæmia.

5. **Cases Presenting both in the Blood and the Blood-making Organs a Group of Changes which More or Less Recall the Disease of Leukæmia.—(Stimulation Myelocytosis).**—(*a*) In various infectious diseases (diphtheria, empyema, scarlet fever) we find sometimes a moderate degree of myeloid change in the marrow or in the lymph glands, with relatively small numbers of neutrophilic myelocytes in the blood. Nothing properly called leukæmia here exists, either in the blood or blood-making organs, but both suggest it. (*b*) In v. Jaksch's disease ("anæmia infantum pseudoleukæmia") we have a collection of various atypical cases of secondary anæmia, pernicious anæmia, (perhaps) splenic anæmia, and pseudoleukæmia, having in common certain points of resemblance to leukæmia, viz., enlarged spleen, circulating myelocytes, nucleated red cells, and anæmia with some increase of leukocytes.

Pseudoleukæmia.—A group of German writers[2] has recently attempted to work out a new concept of pseudoleukæmia as a disease to be distinguished both from Hodgkin's disease and from the conglomerate of various infectious granulomata (tuberculosis, syphilis, etc.). They distinguish pseudoleukæmia as a hyperplasia of specifically hæmopoietic tissue closely akin to leukæmia; in fact, distinguished therefrom solely by the absence of "leukæmic" changes in the peripheral blood. This latter distinction is, however, one of degree, and intermediate forms with slightly or moderately leukæmic blood ("sub-leukæmia") are recognized.

The disease may affect the hæmopoietic system as a whole or in any of its parts (spleen, marrow, or glands), and accordingly medullary, splenic medullary, glandular, and other combined forms are recognized. The number of cases corresponding to these types is small but steadily growing.[3]

Pappenheim regards the disease as sometimes a "forme fruste," sometimes an early stage of ordinary leukæmia, and (in its medullary forms) a transition stage between glandular or splenic pseudoleukæmia (with anæmia)

[1] *American Journal of the Medical Sciences*, 1906, vol. 132, p. 444.

[2] Pappenheim, v. Baumgarten, Sternberg, Benda, and others (see Folia *Hæmatologia*, 1906, p. 453 et seq., and Sternberg, loc. cit.).

[3] Blumer, Ewald, Lesne, and Clerc.

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and true leukæmia. The picture is admittedly indistinguishable from the condition of an ordinary case of *leukæmia in remission* (whether due to infectious complications, *x*-ray treatment, or unknown causes). Obviously some of the cases reported as "leukæmia" are practically identical with the condition here described, and it must also be added (to our confusion) that in some cases of pernicious anæmia the postmortem findings are remarkably like those of "medullary pseudoleukæmia with myelophthisic anæmia" (Pappenheim).

The blood may be (*a*) altogether normal, or (*b*) qualitatively but not quantitatively leukæmic. Without necropsy diagnosis is obviously impossible, for the characteristic changes in the blood-making organs are essential. In symptoms, course, prognosis, and treatment the disease is identical with leukæmia.

Chloroma.[1]—**Definition.**—An atypical form of leukæmia in which green tinted leukoblastic marrow-growths penetrate their bony shell, especially the skull bones, and invade the surrounding tissue.

Conditions of Occurrence.—Up to 1904 there were but 36 cases more or less fully recorded (Dock[2]). As in other types of leukæmia males predominate (29 to 9), but the average age (eighteen years) is considerably younger than in the other forms.

Symptoms and Signs.—1. *The pressure of the tumors produces:* (*a*) exophthalmos, 11 cases; (*b*) deafness, 10 cases; (*c*) swellings in the temporal region, 8 cases; (*d*) blindness, 4 cases; and (*e*) pain, which, especially in the head or legs, is very constant.

2. *Constitutional* (*toxic?*) *manifestations* are early and marked: (*a*) Anæmia in 11 cases, (*b*) early weakness in 9 cases, (*c*) hemorrhages in 8 cases, and (*d*) emaciation in 6 cases.

3. *Visceral infiltrations* are manifested during life in: (*a*) splenic enlargement, 7 cases; (*b*) hepatic enlargement, 3 cases; and (*c*) glandular enlargement (cervical, 11 cases; other glands, 8 cases).

Pathology.—Infiltrating tumors are found frequently in the orbit (12), the dura (9), temporal bone (7), temporal fossa (8), the vertebræ (10), the ribs (8), and the sternum (7); also in the kidneys (12), the liver (8), the marrow (7), the spleen and intestine (each 3), the skin (3), and in many other situations.

With such a multiplicity of points of attack, it is obvious that the various combinations of pressure symptoms, perversions of organic function, and constitutional manifestations make the symptoms too protean and too variable in different cases for any brief or illuminating description.

The Blood.—In almost all the well-studied cases the blood has shown the characteristics already described in the section on acute lymphoid leukæmia. In at least 2 cases, and possibly in 1 other, the blood has been that of myeloid leukæmia. We must therefore recognize myeloid as well as lymphoid forms of chloroma.

The *course of the disease* is short, five and one-half months being the average duration under observation and eighteen months the longest known case.

[1] Türk, *Ein System der Lymphomatosen.* Klein and Sternhaus, *Zentralb. f. path. Anat.*, 1904, p. 49. Sternberg, *Path. der Primarerkrankungen des Lymph. u. Hematopoet. Apparat. Wiesbaden*, 1904, p. 156.

[2] *Transactions of the Association of American Physicians*, 1904, p. 64.

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LEUKANÆMIA.

This is a term coined by Leube,[1] in 1902, and since retained in the vocabulary of medical teachers because it recalls and pictures the confusion which the study of a recent group of cases has produced in hæmatological theory and terminology.

Our dilemma is this: Cases occur in which the blood picture is partly that of leukanæmia and partly that of pernicious anæmia, while the postmortem findings are also more or less equivocal. To these cases Leube gives the name "*leukanæmia*," moved thereto by the following observation: A boy, aged ten years, succumbed after but two weeks' illness to an intense anæmia (red cells 256,000 per cmm., color index 2, megaloblasts predominating over normoblasts). The leukocyte formula strongly suggested acute myeloid leukæmia (leukocytes, 10,600; neutrophilic myelocytes, 13 to 15 per cent.; eosinophiles, 0.8 per cent.; small lymphocytes, 22 to 35 per cent.; polynuclears, 44 to 53 per cent.). The spleen, liver, and bone-marrow presented postmortem essentially the appearances of ordinary myeloid leukæmia. There were no deposits of iron.

Since 1902 about a dozen cases have been published under the title of leukanæmia, and both before and since 1902 a number of other and very similar cases have been published under different names, such as "atypical leukæmia" (Herschfeld[2]), "splenomegaly with anæmia and myelæmia" (Weil and Clerc[3]), aplastic leukæmia (pseudoleukæmia).

All the published cases fall into three groups:

1. Those identical with pernicious anæmia in most respects, but showing some minor deviations.

2. Those identical with leukæmia in most respects, but showing some minor deviations.

3. Those in which the traits of leukæmia and of pernicious anæmia are so evenly balanced that they present a genuine difficulty in diagnosis.

Before examining in detail the reported cases, certain of the known facts about leukæmia and pernicious anæmia should be recalled.

Facts about Leukæmia.—1. That toward the end of most cases of leukæmia the supervention of an intense anæmia, with few, many, or most of the marks of pernicious anæmia, is the rule and not the exception. We should not think of saying merely on this account that most leukæmic cases become "leukanæmic" before death.

2. That toward the end of some cases of leukæmia with complicating infections the number of white cells falls nearly or quite nearly to normal, while the already existing anæmia becomes intensified.

3. If one chanced to see a case of ordinary leukæmia for the first time after (*a*) the supervention of the terminal anæmia, or (*b*) the terminal fall in the leukocyte count, one would be in the presence of most of the evidence on which the diagnosis of "leukanæmia" is usually based. Yet such a diagnosis would seem quite unnecessary to one who had watched the patient in the previous non-anæmic, typically leukæmic stage.

4. "Acute" cases of leukæmia, both of the lymphoid and (less often) of the myeloid type, are not uncommon. Many of those already reported are practically identical with some of the cases recently printed under the title "Leukanæmia."

[1] *Deutsch. Klinik.*, 1902, Nr. 42.
[2] *Folio Hæmat.*, 1904, No. 3.
[3] *Soc. de Biol.*, June, 1904.

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Facts about Pernicious Anæmia.—Approaching next from the other side of the difficulty, we note: 1. That in the blood of most patients with pernicious anæmia there is present sooner or later a small percentage of myelocytes. In the writer's series these were cases showing 0.5 per cent., 2 per cent., 3.5 per cent., 5 per cent., 7 per cent., and 10 per cent.

2. That in the marrow, sometimes also in the spleen, of cases of pernicious anæmia we often find a proportion of myelocytes larger than is present in health.

3. That a marked terminal lymphocytosis has been repeatedly found in patients who for years had run the course and shown the blood typical of pernicious anæmia.

4. Finally, we must remember that in children any influence which stimulates any part of the marrow to activity (*e. g.*, infection, anæmia, toxic states, leukæmia) is prone to rouse the *whole* marrow in greater or lesser degree. Thus infectious leukocytosis in infancy is often accompanied by a "shower" of nucleated red cells, and any type of anæmia is apt to be accompanied by leukocytosis, enlarged spleen, and even myelæmia. Hence leukæmia or pernicious anæmia in children or young people is especially likely to approach that apparent fusion of the two diseases which is suggested in the word "leukanæmia."

Bearing in mind, then: (1) How much there is and has long been in the classic picture of leukæmia to remind us of pernicious anæmia. (2) How much there is in the classic picture of pernicious anæmia to remind us of leukæmia. (3) How prone is the child's hæmopoietic system to give a general response to a special stimulus—to function as a whole with less of differentiation and specialization that we expect in the adult—we may conclude that *with very few exceptions the cases reported as leukanæmia can be thrust back into the old categories.*

Most of the cases reported under the title "Leukanæmia" seem to the writer to be *leukæmia*, more or less atypical, but still leukæmia. In this group belong the cases of Hirschfeld,[1] Drysdale, Kormoczi, Kerschensteiner, Luce, and Mattirolo. The cases reported by Leube, Weber, and Bushnell and Herter may be classed as pernicious anæmia.

Until some more definite criteria are furnished whereby we can distinguish the cases of "leukanæmia" from the leukæmias with terminal anæmia and from the pernicious anæmias with lymphoid or myeloid marrow, there seems no reason why the term leukanæmia should be adopted, and we may hope that (like the anæmia infantum pseudoleukæmia) it may be allowed to perish by disuse.

POLYCYTHÆMIA (ERYTHROCYTOSIS MEGALOSPLENICA).[2]

In 1892 Rendu and Widal called attention to a new symptom-complex in which they noted (1) chronic cyanosis due to polycythæmia, and (2)

[1] The literature of "leukanæmia" is summarized in the articles by Hirschfeld, *Folia Hæmatologia*, 1906, p. 332; by Drysdale, *Quarterly Journal of Medicine*, October, 1907, and by Kerschensteiner, *Münch. med. Woch.*, 1905, Nr. 21.

[2] Englebach and Brown, *Journal of the American Medical Association*, October 20, 1906 (contains an excellent bibliography of the references up to that date). Watson, *Liverpool Medico-Chir. Journal*, July 19, 1906. Köster, *Niiond med. Woch.*, 1906, liii, 23. Senator, *Zeit. f. klin. Med.*, vol. lx, p. 357. Hirschfeld, *Therap. de Gegen.*, vol. xlvii, Nr. 8. Weber, *Lancet*, November 24, 1906. Aldrich and Crummer, *Journal of the Americam Medical Association*, April 6, 1907.

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splenic enlargement. The condition was attributed by them (in this and in a subsequent publication) to primary *splenic tuberculosis*. Vaquez, in 1899, Türk, in 1902, and Osler, in 1903, brought the syndrome into general notice, showed that there was no reason to attribute it to splenic tuberculosis, and gave grounds for believing that the disease is due to a primary hyperplasia of the erythroblastic bone-marrow. Since that time many other reports have been published, so that there are now at least 50 cases on record.

Age and Sex.—The cases are about equally distributed in both sexes, and occur, as a rule, between the thirty-fifth and the sixtieth year.

Symptoms.—The patients seek advice, as a rule, on account of (1) the abnormal color and condition of the skin and mucous membranes; (2) the symptoms of cerebral congestion (headache, vertigo, etc.); and (3) weakness.

The facial color is a peculiar, mottled, brick-red, with a purplish tint in the lips and ears (a "red Indian," one of the patients was called), but on the unpractised eye the *cyanosis* of the lips, nails, and many other parts makes the strongest impression. Brownish pigmentation may occur. The tongue and buccal mucous membranes are of a deep purple, and hemorrhagic oozing from the gums is a frequent result of the intense congestion and malnutrition.

Other evidence of peripheral congestion is found in—

(*a*) *Hemorrhages* from the nose, stomach, bowel, lung, skin, and genital tract.

(*b*) *Cerebral Disturbances.*—Besides headache and vertigo, which are the commonest and mildest, we have occasionally cerebral hemorrhage (hemiplegia, monoplegia, facial paralysis), paraphasia, muscular spasms, and other paroxysmal attacks.

(*c*) *Facial Neuralgia* (also erythromelalgia in 2 cases).

(*d*) *Dyspnœa and œdema of the lungs.*

Gastro-intestinal symptoms, circulatory, respiratory, and genital symptoms (except as above noted), are not prominent. The urine is often normal, or shows a low specific gravity with or without polyuria, a trace of albumin and hyaline and granular casts in moderate numbers. Urobilin is sometimes present. The fundus oculi is deep red; the veins are enlarged, purple, and very tortuous.

The temperature, pulse, and respirations are usually normal.

Physical Examination.—Besides the points above noted, the most important are (*a*) splenic enlargement, and (*b*) the blood findings. The *spleen* was demonstrably enlarged in at least 85 per cent. of all the cases so far reported. It may fill half of the abdomen, but is usually of moderate size, reaching to or nearly to the level of the navel. The shape of the organ and its notches are preserved. The surface is smooth and hard. Pain, tenderness, and dragging sensations in the splenic region are often complained of.

The Blood.—Viscosity is markedly increased. The *red cells* are usually above 8,000,000 at some period of the disease, and in about one-half of the cases counts of 10,000,000 to 13,000,000 are recorded. The *hæmoglobin* is from 120 to 200 per cent. (19 to 26 grams). The *leukocytes* are also increased, as a rule. About half the cases show over 20,000 leukocytes per cmm. at some period. Still more constant is the increase in the relative (and absolute) number of polynuclear neutrophiles, which in two-thirds of the cases ranged from 75 to 92 per cent., with a proportionate decrease in the percentages of lymphocytes. In Weber's case and a few others there was leukopenia.

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Other *evidences of abnormal marrow activity* are seen in the presence of normoblasts, which are noted in most of the cases in which a careful search for them was made, of megaloblasts (numerous in Aldrich and Crummer's case), and of myelocytes. In the case just mentioned there were 6600 erythroblasts per cmm., a majority of them of the megaloblastic type, and 211 myelocytes (4.5 per cent.) per cmm. The large mononuclear (marrow?) lymphocytes are also increased (11 to 24 per cent.) in most cases. The red cells occasionally show variations in size, shape, and staining reaction. The blood plates are usually increased. *Enlargement of the liver* has been noted in the majority of cases, but it is decidedly less striking than the splenomegaly. *The muscular and mental weakness* is constant and usually progressive. There are not infrequently attacks of sudden prostration, faintness, or giddiness, as in Ménière's disease.

Pathology and Pathogenesis.—The number of autopsies is still small. Splenic tuberculosis was present in the earliest French cases, but not in most of those later reported. Its etiological significance is dubious. Widal believes that by the loss of functioning splenic tissue the activities of the marrow are abnormally stimulated, so that hyperplasia and polycythæmia resulted. Vivid purple marrow, with erythroblastic and leukoblastic hyperplasia, is the most constant anatomical finding. In the femur of Watson's case the compact bone was slightly encroached upon and the shaft was abnormally brittle. Rosengart found also evidence of erythroblastic and leukoblastic metaplasia in the spleen and liver of one case. On the other hand, "normal marrow" (microscopically) is reported in Saundby and Russel's case, and Watson found only intense vascularity and congestion in the spleen.

Rechzeh considers blood stagnation from diminished venous tonicity as the cause of the disease, but his reasons and experiments do not seem convincing.

Diagnosis.—The commoner causes of cyanosis—cardiac and pulmonary disease, local pressure or paralysis, methæmoglobinæmia and other intoxications, intestinal fermentation, etc.—must be excluded. This done, the presence of marked polycythæmia with enlarged spleen is sufficient, although not absolutely certain evidence of the presence of the disease. The existence of tuberculosis in the spleen or elsewhere in the body does not negative the diagnosis of primary polycythæmia.

Prognosis and Course.—Recovery has not yet been reported, but in some cases the disease lasts for many years; six to eight years is the average, although one of Türk's patients died in three months.

Treatment.—Bleeding gives marked although temporary relief. Splenectomy has been several times performed, but not with results that justify us in advising the operation, especially as the not infrequent hemorrhagic tendency in the disease increases the already considerable operative risk. Herschfeld advises the iodides.

X-ray treatment has given on the whole the best results. The size of the spleen and the blood count may be considerably reduced and the patient's condition improved. The technique is similar to that advised in myeloid leukæmia.

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CHAPTER XVI.

PURPURA AND HÆMOPHILIA.

By JOSEPH H. PRATT, M.D.

PURPURA.[1]

PURPURA is the name applied to spontaneous hemorrhages developing in and beneath the skin and mucous membranes. It is a symptom seen in a variety of pathological conditions. In idiopathic or primary purpura, spots of cutaneous hemorrhage constitute the chief symptom, the cause of which is at present unknown. Thus the term purpura is used to indicate both a symptom and a disease. The disease purpura or morbus maculosus may be defined as a condition characterized by an acquired hemorrhagic tendency, usually transitory, which manifests itself by hemorrhages into the skin or from the mucous membranes, or both combined.

The true nature of purpura and its mode of production are unknown. Its etiology and pathology have been little extended since Willan wrote his classic work ninety-nine years ago. Dr. Osler has referred to purpura as "that obscure and interesting manifestation of which we know so much and at the same time so little." The symptom purpura may occur in hæmophilia and scurvy. In the disease purpura the hemorrhagic tendency is not congenital or hereditary, in contrast to hæmophilia; neither does it occur epidemically or endemically, as is the case with scurvy.

Historical.—Purpura (*πορφύρα*, purple) was the name applied by the ancients to the eruption of scarlet fever and measles as well as to hemorrhages into the skin. Riverius appears to have been the first author who attempted to separate purpura from the petechial fevers. The designation *morbus pulicaris sine febre* was given to it by Lusitanus about the year 1550. Zeller, professor of medicine in Tübingen, published in 1694 a clear description of purpura. The older writers confused it with scurvy. The name morbus maculosus was applied by Werlhof. In his "Opera Medica" a well-marked case of purpura in a young girl is recorded; she had in addition epistaxis and hæmatemesis. Wichmann, who edited Werlhof's papers, sought to make a sharper distinction between purpura and petechial fever. The name peliosis was given by Schönlein to designate what he considered to be a distinct clinical condition.

Classification.—Our ignorance of the true nature of the purpuras is shown in the widely varying views held in regard to their proper nosological

[1] The writer was aided in the preparation of this article by material placed at his disposal by Dr. Osler, consisting of the notes of many private cases, unpublished lectures, and abstracts of articles in the literature. The statistical data is based largely on the clinical records of the Massachusetts General and the Johns Hopkins Hospitals.

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position. Some writers deny the existence of purpura as an essential disease, and refuse to admit that cases developing without apparent cause and presenting symptoms in common should be regarded as a clinical entity. They look upon it solely as a cutaneous eruption accompanying a number of morbid states. This view has been set forth recently by Barbier.[1] The title of his article is not "Purpura," but "The Purpuras." It was advanced as long ago as 1874 by Mollière,[2] and has been held many years by Stephen Mackenzie.[3]

Hoffmann, Litten, and most other German writers embrace all the primary purpuras under the denomination "Morbus maculosus Werlhofii," of which purpura simplex is the mildest and purpura hæmorrhagica the gravest type. W. Koch goes still farther and maintains that scurvy, hæmophilia, and morbus maculosus are different manifestations of one and the same disease. The writer knows of no recent author who accepts this view, and there is general agreement that scurvy and hæmophilia are clinical entities.

Those who regard purpura as only a symptom are obliged to admit that in many cases the purpura is primary with no associated condition or cause to which it might be attributed. In 200 cases of purpura analyzed by S. Mackenzie,[4] and arranged as regards probable cause, no less than 68 were tabulated as "unexplained." If to these be added the cases with arthritis, 71 in number, it will be seen that 70 per cent. of his cases of "symptomatic purpura" might be classed as idiopathic or primary purpuras. It is highly probable that the morbus maculosus of the Germans includes several distinct disorders. It is possible, however, that purpura simplex and purpura fulminans simply represent a mild and severe form of the same affection. In purpura simplex a few small spots of hemorrhage on the legs may be the only sign of disease, while purpura fulminans usually runs its course and ends in death within twenty-four or forty-eight hours.

It is true that purpura is the name of a symptom, but this is not sufficient reason for refusing to apply this term to idiopathic cases in which cutaneous hemorrhage is the dominating and primary feature in the disease-picture. Anæmia is a symptom and not a disease, yet cases of severe progressive anæmia developing without any discoverable cause are grouped together under the term primary pernicious anæmia.

Secondary Purpura.—Purpura in Acute Infectious Diseases.—It may occur during the course of any infectious disease, and in typhus fever the eruption is always purpuric. It is not uncommon in smallpox and cerebrospinal meningitis; in fact, purpura is more frequent in smallpox than in any other of the acute exanthemata. Bancroft observed twelve examples of hemorrhagic variola among 1200 cases of smallpox. It is seen particularly in the early stages of the disease before the characteristic eruption appears. In ulcerative endocarditis the occurrence of purpura is so common as to be of diagnostic value. The hemorrhagic variety of scarlet fever and measles is rare, but less so than that of typhoid fever. Purpura may result from vaccination.

Purpura in Chronic Disturbances of Nutrition.—Cases of this type are often described under the heading of cachectic purpura. Purpura

[1] Grancher et Comby, *Traité des maladies de l'enfance*, deuxième edition, tome premier, Paris, 1904.
[2] *Ann. de Dermat.*, 1873–1874, v
[3] *British Medical Journal*, 1883.
[4] *Allbutt's System of Medicine*, 1898, vol. v.

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may develop in Bright's disease, heart disease, pernicious anæmia, general disturbances of nutrition, cancer, Hodgkin's disease, leukæmia, tuberculosis, icterus gravis, chronic alcoholism, and other conditions. In pernicious anæmia the writer has seen an extensive extravasation of blood into the subcutaneous tissues of the thigh, producing induration of almost stony hardness (scorbutic scleroderma), which extended from Poupart's ligament to near the level of the knee. Severe purpura hæmorrhagica has been repeatedly observed in lymphatic leukæmia.

The occurrence of the hemorrhagic diathesis in chronic nephritis deserves special consideration. A woman was admitted to the Carney Hospital, Boston, with acute nephritis, and died three weeks later. At the autopsy, copious hemorrhages into the intestine, bronchi, and uterus were found. Purpura cannot be considered as a common complication of nephritis, and Bamberger observed only 5 cases among 2430 cases of renal disease. It should be remembered that all forms of purpura are rare. The table prepared by S. Mackenzie from the records of the London Hospital showed that in that institution purpura occurred more frequently in nephritis than in any other chronic disease. Analysis of our series of cases brought to light the same fact. Riesman[1] has reported 2 cases, both ending fatally.

According to Bensaude et Rivet,[2] chronic purpura is not uncommon in tuberculosis. Among their 36 cases of chronic purpura hæmorrhagica, 7 occurred in tuberculous subjects, while in 5 more tuberculosis probably existed.

Senile Purpura.—The term purpura senilis was given by Bateman, who was the first to recognize the condition. "It appears principally along the outside of the forearm, in successive dark-purple blotches, of an irregular form and various magnitude" (Bateman[3]). To the same type of eruption the name purpura cachectica[4] has also been given. The backs of the hands and the forearms are more frequently involved than in any other form of purpura. The purpuric patches are usually of larger size than in the other forms of symptomatic purpura; it is doubtful if this form is as common as statements in the text-books indicate, and Bateman saw only a few cases.

Toxic Purpura.—Iodine heads the long list of drugs that may under exceptional conditions produce purpura. The iodides do not give rise to purpura except in individuals with marked idiosyncrasy. It is of very rare occurrence considering the extensive use of the iodides in medicine. Not a single case of iodic purpura was found in the records of the Out-patient Department of the Massachusetts General Hospital among the 96,600 patients treated there in the past four years. All forms of drug purpura are rare. Three cases represent the number occurring at the London Hospital in a period of sixteen and a half years.

Grossman[5] reported a case in which epistaxis occurred after iodine had been taken for five days and petechiæ appeared two days later. After the purpura disappeared half a gram of potassium iodide was given one morning,

[1] *American Journal of the Medical Sciences*, November, 1907.
[2] *Presse Méd.*, 1906, xiv, p. 469.
[3] *Practical Synopsis of Cutaneous Diseases*, third edition, London, 1814.
[4] Matthieu, *Arch. gén. de méd.*, 1883, p. 273. Voeckler, *Deutsche med. Wochenschrift*, 1904, Nr. 23.
[5] *Rev. prat. d. mal. cutan.*, 1906, v, p. 231.

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and on the evening of the same day a new crop of purpuric spots developed. Although usually a benign affection, grave symptoms may arise, and death may occur. S. Mackenzie has recorded a case in which fatal purpura resulted from a single dose of 2.5 grains of potassium iodide in an infant five months old.

A remarkable case of iodic purpura was seen in the Boston City Hospital. The fingers were swollen and covered by large hemorrhagic blebs, while on the tip of the nose was a black necrotic area 2 cm. in size. Over the thighs was a typical purpuric eruption with spots 0.5 to 1 cm. in diameter. The patient had been given 180 grains of potassium iodide during a space of four days for rheumatoid pains. At the end of that time the purpura and the blebs on the fingers developed. Dr. Osler refers in his text-book to an instance of acute febrile purpura due to iodine. In this patient there was an extensive urticarial rash associated with the purpuric spots. It is said that the lesions in drug purpuras show a greater tendency to become gangrenous than in purpura induced by other causes. These 2 cases of iodic purpura are the only instances of so-called toxic purpura in the present series. E. Wagner says that mercury stands next to iodine in the frequency with which purpura follows its use. He states that mercury given as an inunction is more liable to cause purpura than when administered internally. He was obliged to abandon that form of mercurial treatment several times owing to hemorrhages from the nose and mouth as well as into the skin. Bateman refers to a case of mercuric purpura which resulted in death. Rudaux[1] has reported a fatal instance of purpura hemorrhagica apparently caused by a single large dose of antipyrine. Other drugs said to produce purpura are chloral hydrate, copaiba, quinine, belladonna, arsenic, turpentine, phenacetin, ergot, and salicylic acid. Snake venom produces hemorrhagic extravasations with great rapidity.

Nervous Purpura.—There are well-authenticated instances of purpura developing after severe fright in individuals of nervous temperament. Probably neuropathic influences are concerned in the production of the purpuras characterized by periodic recurrence. A case of this rare type was observed at the Massachusetts General Hospital. The patient, a woman aged twenty-eight years, in place of the menstrual flow had an attack of vomiting every three weeks for a period of more than a year. For five months previous to her admission the vomiting had been accompanied by a copious purpuric eruption on the arms, legs, and trunk. The vomitus never contained blood. On examination purpuric spots were found on the parts mentioned. Some of the hemorrhages were about 4 cm. in size. She was seen eighteen months later in a similar attack. Cazenave observed a periodical monthly purpura in a young girl who had never menstruated. Apert[2] reported a case in a man who had hemorrhages from the rectum recurring regularly every month for six years. Except during the first two years, each attack was accompanied by a crop of purpura. W. S. Thayer[3] has observed this monthly recurrence of bleeding in 2 cases of telangiectasis. In a case described by Trousseau, an eruption of purpura urticans accompanied each menstruation for a year or more. Purpura occurring during pregnancy (Brieger) and childbirth probably does not belong in this group.

[1] *Comptes rendus de la Soc. d'Obstét., de Gyn. et de Péd. de Paris*, October, 1903, v.
[2] *Bull. méd.*, 1899, p. 9.
[3] Personal communication.

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Weir Mitchell reported 3 cases characterized by severe neuralgia and muscular spasms in which purpuric spots appeared at or near the painful points. Bouchard has observed purpura in trifacial neuralgia, and Faisans in sciatica. Purpura has been described in connection with the lightning pains of tabes (Straus), in hemiplegia on the paralyzed side (Gibert), and in multiple sclerosis (Chevalier).

The remarkable condition known as stigmatization, in which hemorrhage occurs from the unbroken skin, belongs in this group. The subject is well presented in Hoffmann's "Constitutionskrankheiten." Imbert-Gourbeyre has collected 153 instances chiefly from the literature of the Church.

Hæmatidrosis.—Tittel observed a case in which blood spurted in little streams from the sweat glands. This bloody sweat occurred in a strong man otherwise quite well. Microscopic sections through the skin showed red blood corpuscles in the sweat ducts. Hoffmann says that this is the only instance on record in which the proof is complete. Heubner refers to a true bloody sweat affecting the backs of the hand and the tips of the fingers. In the orifices of the sweat ducts appeared small drops of blood which flowed over the surface of the skin. This strange symptom recurred periodically.

Mechanical Purpura.—The hemorrhagic spots that may appear after an epileptic seizure or a paroxysm of whooping-cough are of this type. Numerous petechiæ are sometimes produced on the knee by the application of a tight bandage around the lower portion of the thigh. Bramwell regards the purpuric eruptions which develop on the dropsical lower extremities in the terminal stages of cardiac disease as frequently mechanical in origin.

The fact that the eruption in every form of purpura is almost always more abundant on the legs than elsewhere is probably the result of mechanical influences. Attempts to sit up after an attack of purpura may be followed by the appearance of a new crop on the legs. *Purpura orthostatique* is the name given by Archard and Grenet[1] to this condition. A striking example of this type was under observation at the Massachusetts General Hospital in a woman aged twenty-four years. Three weeks prior to her entrance she had been suddenly seized with pain and swelling in both feet. A large crop of purpuric spots covered the feet and lower legs. She states that since the onset new blotches appeared, accompanied by swelling of the feet and severe pain, whenever she attempted to sit up or walk. The day after admission the spots had almost entirely disappeared, so she was placed in a chair with her feet bandaged, but the feet swelled as before and a purpuric rash developed on the heels, which were uncovered by the bandage. Three days later another attempt was made after flannel bandages had been applied to the feet and legs as high as the knees. Purpuric spots appeared on both thighs and on the ankles below the malleoli. One day a fresh crop was produced by moving her to a sofa. For five weeks she was obliged to remain in bed. As long as she was at rest in the recumbent posture no new spots developed. In this case the influence of mechanical factors is clearly shown, yet they were not the primary cause of the condition, for the tendency to hemorrhage was transitory. Hence it belongs in the group of essential or primary purpuras.

Idiopathic Purpura.—Frequency of Occurrence.—Only when the other diseases and toxic conditions have been excluded is the diagnosis of primary

[1] *Soc. méd. des hôpitaux*, January 29, 1904.

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purpura justifiable. At the Massachusetts General Hospital 65 cases of idiopathic purpura occurred among 155,884 medical and surgical in-patients during thirty-three years. At the Johns Hopkins Hospital 41 cases were observed in 18,594 medical patients. At the Hamburg General Hospital there were 73 cases in forty-one years in a total of 100,000 patients (Scheby-Buch). Thirteen cases occurred in the Mary Magdalene Hospital of St. Petersburg during twenty-four years, among 82,000 patients (Masing). S. Mackenzie states that of 63,834 cases in the London Hospital there were 200 cases of purpura. This included symptomatic as well as idiopathic purpura. In the experience of some physicians the disease is more common than these figures indicate. Thus, Bramwell[1] observed 16 cases among 5256 ward patients in the Edinburgh Royal Infirmary, and in 7686 private patients 9 were cases of purpura.

TABLE OF 258 CASES OF PRIMARY AND SECONDARY PURPURA.

	Cases.	
PRIMARY PURPURA:		
Simple purpura	45	
Simple purpura with arthritis	54	
Purpura hæmorrhagica	52	
Henoch's purpura	43	
	—	194
SECONDARY PURPURA:		
	Cases.	
Typhoid fever	10	
Nephritis	8	
Tuberculosis	7	
Heart disease	6	
Lymphatic leukæmia	5	
Ulcerative endocarditis	4	
Rheumatism	4	
Hepatic cirrhosis	3	
Jaundice	3	
Iodic purpura	2	
Carcinoma of gall bladder	1	
Tumor of the liver	1	
Alcoholic neuritis	1	
Nervous purpura	1	
Whitlow	1	
Pneumonia	1	
Arteriosclerosis	1	
Chorea	1	
Chronic arthritis	1	
Pernicious anæmia	1	
Marasmus	1	
Aneurism	1	
	—	64
		258

Etiology.—Sex and Age.—Laache states that purpura simplex and purpura rheumatica occur more frequently in the male sex, especially near the time of puberty. Women are said to be more predisposed to purpura hæmorrhagica than men. The disease is most common in the second decade, 48 (29 per cent.) of this series developing during this period. Among 90,556 sick children Gross found 41 cases. The disease purpura is rare

[1] *Clinical Studies*, Edinburgh, 1905, p. 325.

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after fifty years of age. In this series 129 of the patients were males and 65 females; 27 of the cases of purpura simplex were in males and 14 in females. Purpura rheumatica was more common in males; there were 38 cases in males and 16 in females. Purpura hæmorrhagica occurred 30 times in males and 20 in females.

Seasonal Frequency.—It is asserted that the disease occurs more frequently in the fall and winter, and is more prevalent some years than others. The present series of 194 idiopathic cases observed in Boston and Baltimore offers no support for either of these claims. The Massachusetts General Hospital records analyzed for this purpose cover a period of thirty-four years, and the Johns Hopkins Hospital records eighteen years.

There is no evidence that damp dwellings or a delicate constitution exert any particular influence in the production of purpura. Of course, lowered vitality and poor hygienic surroundings would favor the development of disease. Strong, well-nourished individuals are sometimes struck down with purpura hæmorrhagica while apparently in perfect health.

Heredity.—Förster observed the disease in three sisters. Bauer speaks of a number of families in which several of the members at a certain age suffered from purpura. Dohrn reported a case in which purpura was transmitted from a mother to her newborn child.

Pathogenesis.—In its production the bloodvessels are certainly concerned, and the changes in them may be secondary to alterations in the blood. Recent French investigators hold that disturbance in hepatic function is an important factor in the production of the disease. The experimental studies of Grenet indicate that the primary cause of purpura is the action of some toxin on the central nervous system. The view that purpura is an infection has had many advocates. Streptococci and staphylococci have been repeatedly found in the secondary purpuras of septicæmia. In idiopathic purpura, however, blood cultures have been repeatedly made by recent investigators with negative results.

Relations of the Bloodvessels to Purpura.—The vascular alterations that have been observed at autopsy are not constant, and seem to throw little light on the cause of idiopathic purpura. Riehl described the presence of localized degeneration of the vessels in all forms of purpura. v. Kogerer claimed that careful search would always reveal the presence of thrombi due to vascular degeneration. According to this theory, disease of the vessels led to thrombosis, and this in turn to the hemorrhages. v. Recklinghausen shared this view, and it probably does explain the origin of cutaneous hemorrhages in some cases of arteriosclerosis. Oriou, one of Hayem's students, has described a rare type of purpura in which the spots result from the obliteration of cutaneous vessels, and are true infarcts. In this variety, of which Oriou reported only one case, the spots are prone to become gangrenous. Cornet examined the skin in two cases that were diagnosed clinically as purpura, and found not hemorrhages, but a localized dilatation of the vessels. Emboli composed of micrococci have been observed in malignant endocarditis occupying the centres of the purpuric spots. They have been recognized by the naked eye as white points. Even in malignant endocarditis they are rare, and in idiopathic purpura emboli are never observed in association with the purpuric spots. Litten carefully examined microscopically many specimens of cutaneous and retinal hemorrhages, but could discover no changes in the vessels to which they might be attributed.

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Whether the erythrocytes leave the vessels by rhexis or diapedesis is not known. Many pathologists have examined purpuric spots without finding any breaks in the vascular walls. Unna claims, however, that the small veins rupture, and that the tear usually occurs at the junction of the cutis and the subcutaneous tissue. At this point their adventitia is lacking and they have not the support of the dense elastic cutis. His observations have not been confirmed. Clinicians have objected to the theory of primary vascular degeneration as a cause of typical purpura hæmorrhagica, for the reason that the hemorrhages are widely distributed over the surface of the body and often develop with great rapidity. Such a generalized and speedy alteration of the vessels has seemed improbable. Furthermore, the tendency to hemorrhage is transitory. Hence it is difficult to reconcile the clinical picture of a severe, rapidly developing disease of short duration with a serious disease in the vessels. If purpura is due to endarteritis and hyaline degeneration of the vessels, one would expect that the hemorrhages would continue indefinitely. It is possible, however, that the vascular injury may consist of a fatty metamorphosis, which is frequently of short duration and may be followed in the heart and liver by complete restoration of structure and function. Flexner discovered a substance in snake-venom possessing the property of destroying endothelium, and to which he gave the name hemorrhagin. The injection of snake-venom into laboratory animals is followed in a few minutes by multiple hemorrhages. The hemorrhagins contained in different venoms are not identical. Gay and Southard found in their study of anaphylaxis that hemorrhages occur with extraordinary rapidity, and focal fatty changes with hemorrhage are observed in as short a time as four minutes. They assert that at least a part of the hemorrhages in their experiments were due to endothelial changes in the capillaries. These studies are certainly suggestive that in purpura there may be some substance in the blood that produces an endotheliolysis with focal hemorrhages.

Changes in the Blood.—Considerable evidence can be adduced in favor of the view that purpura is due to a pathological condition of the blood.

The Blood Platelets.—A Belgian histologist, Denys, noticed in a case of purpura hæmorrhagica an almost complete absence of blood platelets. In 1890, Hayem observed a case of purpura in which the blood likewise showed a remarkable diminution in the number of platelets. The red count was 6,020,000, while the platelets numbered only 69,000 per cmm. The normal number of platelets as determined by Hayem was 250,000. In his *Leçons sur les Maladies du Sang*, published in 1900, he reported 3 additional cases, in all of which the number of platelets was greatly diminished. His lowest count was 42,000. Ehrlich[1] makes the statement that in a case of purpura hæmorrhagica studied by him the number of platelets was greatly diminished and Bensaude concluded, after examining a large number of cases, that diminution of platelets is characteristic. These observations of Denys and Hayem are not mentioned even by recent writers on purpura.

Helber found the blood platelet count reduced to 40,000 in a case of purpura hæmorrhagica. The patient, a girl aged fourteen years, had severe hemorrhage in the skin and from the mucous membranes. The erythrocytes were 4,300,000, leukocytes, 12,000, and blood platelets, 40,000.

[1] *Die Anämie*, Vienna, 1898, p. 134.

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The writer has shown elsewhere that the methods of counting blood platelets employed by Hayem and Helber yield too low results, but their observation that the blood platelets are greatly diminished in some cases of purpura hæmorrhagica he has been able to confirm. A much more reliable method was devised for enumerating the platelets,[1] and it was found in severe purpuras that the platelets were almost absent. In a case of severe symptomatic purpura occurring in chronic nephritis there was a greater reduction in the number of platelets than has been observed in any other condition, and the writer's counts in 3 cases of purpura are lower than any reported. The average number of blood platelets in health as determined by this method is 469,000.

In the case of nephritis just mentioned death was due to the hemorrhagic diathesis. When admitted the patient had had recurrent epistaxis and hemorrhages from the lips and mouth for three months. A purpuric rash was present at the time of the first blood examination on November 19. The erythrocytes were then 2,520,000; the blood platelets, 16,000. On November 21 the erythrocytes were 2,608,000, but the number of plates had dropped to 7000. On November 22 it was noted that the hemorrhage from the gums had been almost continuous since the previous day, and the face and hands were blanched. The lips and gums were covered with dried blood, and there was a steady oozing of blood from the gums. On the lobe of the ear at the site of puncture was a thick layer of clotted blood. The patient was nervous and excited, fearing he would die. The erythrocytes were reduced to 1,520,000 per cmm., and the blood platelets to 9000. It was interesting and significant that a sudden diminution in the number of the blood platelets preceded the severe hemorrhage.

The writer saw, with J. W. Coe, a patient with chronic purpura hæmorrhagica in whom the blood-platelet count was found to be 29,000 per cmm., and in another they were reduced to 22,000. Coe[2] has reported 5 severe cases of the hemorrhagic diathesis, in all of which the one constant feature was the very small number of blood platelets. Carefully studying the bloods from day to day, he was led to the conclusion that there is a close relationship between the small number of platelets and the liability to hemorrhage. In one patient the sudden disappearance of the plates from the stained films suggested, fully forty-eight hours before bleeding began, that it was about to recur.

Blood from another patient taken the day on which the severest attack of hemorrhage occurred showed "total absence of plates" in the stained specimen, whereas they had previously been present, although in much diminished number. In a mild case of acute purpura hæmorrhagica the writer found some reduction in the platelet count, although it was not made until convalescence had begun. In simple purpuras the number of platelets in the few cases observed has been normal.

Purpura is not the only condition in which the blood platelets are greatly diminished. In lymphatic leukæmia a low count is the rule. In pernicious anæmia the number is reduced, but in less degree. In both these conditions severe purpura is a well-recognized complication. Gley[3] found that injec-

[1] *Journal of the American Medical Association*, December 30, 1905.
[2] *Ibid.*, 1906, xlvii, p. 1090.
[3] *Soc. de biol.*, December 19, 1896.

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tions of albumose into the circulation of animals diminished the number of platelets. Krehl and the writer made a similar observation. The small number of blood platelets in purpura might be due either to diminished production or increased destruction. Hayem produced a condition which he considered somewhat analogous to purpura hæmorrhagica by the injection into the vessels of serum from an animal of a different species. The blood platelets collected together in masses, and these formed thrombi; very few platelets were left in the circulating blood. Hayem thinks this experiment teaches that the diminution of plates is due to increased destruction. He suggests the possibility that toxins may be introduced into the blood from the digestive tract. This view of an auto-intoxication from the intestine is also held by Ajello, who found methæmoglobin in the blood in one case of purpura hæmorrhagica.

In the hemorrhagic form of scorbutus Hayem found no reduction in the number of platelets. This supports the present teaching that purpura hæmorrhagica and scurvy are different diseases.

Relation of Blood Platelets to the Coagulation of the Blood.—In an investigation made by Krehl and the writer no direct connection could be discovered between the number of blood platelets and the coagulation time. According to the present teaching, thrombin (fibrin ferment) is produced from thrombogen (prothrombin) by the action of calcium salts and zymoplastic substance (thrombokinase). Thrombin unites with fibrinogen to form fibrin. Thrombokinase is present in all the cells of the body. Morawitz[1] found, on the other hand, that blood platelets are the only cellular elements of the blood that contain thrombogen. The addition of disintegrated blood platelets to a mixture of cellular extract (thrombokinase) and fibrinogen caused marked acceleration of the coagulation time. In his later papers he seems to attach less importance than formerly to the part played by the blood plates in coagulation, and he now regards the plasma as the chief source of thrombogen. Ducceschi[2] says that small, grape-like masses composed almost entirely of blood plates form on the cut edges of vessels immediately before coagulation. They would tend to close the wounds in small vessels and thereby check bleeding.

Contraction of the Clot.—Hayem has described another remarkable alteration of the blood in purpura. Normally a blood clot quickly contracts and expresses serum. The clot in purpura hæmorrhagica, he claims, does not retract, and there is no extrusion of serum. Millard, Apert, and Lenoble have confirmed this observation. It is strange that this remarkable modification of coagulation has attracted little attention outside of France. The test is performed as follows: About 3 cc. of blood is collected in a small test-tube. Normally the surface of the clot becomes concave in about fifteen minutes. At the end of an hour it begins to be separated from the wall of the test-tube. At the end of twenty-four to forty-eight hours the contraction should be complete and the clot entirely surrounded by a layer of serum. Occasionally it remains fastened to one side of the wall. In the first case of purpura in which Hayem found the platelets greatly reduced in number, the blood clotted in five minutes. At the end of twenty-four hours, however, there was no contraction of the clot and no expression of serum. In the other cases similar observations were made. According

[1] *Deut. Arch. f. klin. Med.*, 1904, lxxix, p. 215.
[2] *Il Policlinico*, No. 15, ref. *Biochem. Zentralbl.*, 1903, i, Nr. 12.

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to Hayem the pathognomonic characteristics of true purpura hæmorrhagica are the rarity of the blood platelets and the absence of expression of serum after coagulation of the blood.

Hayem made an experiment to test the role of the blood plates in the contraction of the clot. The jugular of the horse was removed between two ligatures and suspended vertically in the cold to retard putrefaction. The erythrocytes and leukocytes sank to the lower part of the column, while in the upper portion the blood platelets and some leukocytes floated in the plasma. A part of this plasma rich in platelets was put directly into a test-tube. The remainder of the plasma was filtered at 0° C. in order to remove the blood platelets, and placed in another test-tube. The unfiltered plasma coagulated quickly. The clot contracted and expression of serum occurred. The filtered portion coagulated more slowly, and the clot did not contract and no serum appeared. The filtered specimen differed from the other only in the absence of platelets. It is, hence, natural to ascribe contraction of the clot to the blood platelets. Hayem reports a case in which a *crise hematoblastique* (sudden diminution in the number of platelets) coincided with sudden development of this modification in coagulation.

Failure of contraction occasionally occurs in symptomatic purpura. This alteration was observed by Hayem in a tuberculous subject without hemorrhage from the mucous membranes. There were very few platelets in the blood and the clot did not transude any serum. He says that the absence of contraction is seen in certain infectious states without any diminution in the number of platelets. According to Hayem's view, substances exist in certain toxæmias whose presence gives rise to an abnormal fibrin that has lost its property of contraction. Grenet[1] studied 4 cases of purpura in which the clot contracted in a normal manner, but no observations were made in regard to the number of platelets. Apert and also Allacia found no diminution of platelets and normal retraction of the clot. Contractility is favored by the addition of liver extract to the blood (Gilbert and Weil).

Le Sourd and Pagniex,[2] in a recent paper, state that this phenomenon—failure of the clot to contract—has been repeatedly observed when the number of blood platelets is increased. Nevertheless, on the basis of the experimental work, they attribute contraction of the clot to the blood platelets. They found that clots formed by the coagulation of oxalate plasma, rennin plasma, and hydrocele fluid do not contract. If one adds blood platelets to them they produce clots that do contract, and the degree of contractility varies with the number of platelets added. This property of the blood platelets is thermolabile. It is impaired by heating to 45° to 50° and destroyed at 58° C. A serum that destroys blood platelets can be obtained by injecting blood platelets from rabbits into guinea-pgs. Such a serum checks the contraction of the clot. If this serum is introduced into the circulation of the living animal, it reduces the number of blood platelets and renders the blood clot less contractile.

The Coagulation Time in Purpura.—In the majority the blood coagulates within the normal time. In one case of fatal hemorrhage from the mucous membranes the coagulation time as determined by the method of Brodie and Russell was four minutes. In this series there are 34 cases of idio-

[1] *Tribune méd.*, 1903, xxxv, p. 438.
[2] *Journ. de phys. et path. gén.*, July 15, 1907, lx, No. 4.

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pathic purpura in which the coagulability of the blood was determined. These observations were made in the Johns Hopkins and Massachusetts General Hospitals. The average time in this series was five and a half minutes. Brodie and Russell's method was the one chiefly employed. Hinman and Sladen,[1] in a careful study, have shown that with the Brodie-Russell method records below seven to eight minutes are normal. In several instances in our series the clotting was retarded, in one case to fourteen and a half minutes, and in another thirteen minutes, but no direct connection could be traced between delayed coagulation and the severity of the hemorrhagic tendency. Both Litten and Hayem state that the coagulation time in purpura is not diminished. Doubtless exceptions to this rule occur. Morawitz has observed a case in which there was an extraordinary delay in the coagulation time. The hemorrhagic diathesis in cholæmia differs in this respect from that in idiopathic purpura; thus in a case of obstructive jaundice with hemorrhages the coagulation time was found by the writer to be over one hour by the Brodie-Russell method. Hinman and Sladen observed greater retardation of the coagulation time in malignant jaundice than in any other condition.

These studies of the coagulation time in purpura would indicate that there is no marked deficiency in thrombin or its antecedents, thrombinogen or thrombokinase. Although clotting occurs in cases of purpura with severe hemorrhage, it is noted that the clots are sometimes less firm than normal. It is possible that fibrinogen, the mother substance of fibrin in the blood, is decreased or that there is an increased fibrinolysis. As Dastre has shown, the coagulation time is no index to the amount of fibrinogen present.

Changes in the Liver.—There are many observations which tend to show that there is some connection between hepatic function and the normal coagulation of the blood, particularly some relation between fibrinogen and the liver. It was shown many years ago that by shutting off the abdominal circulation the blood became non-coagulable. Doyen found that injury to the liver parenchyma, as well as extirpation of the organ, quickly rendered the blood non-coagulable, and that lack of fibrinogen was the cause of the failure of the blood to clot. Doyen claims that fibrinogen is chiefly formed in the liver. After destruction of the liver there is a rapid disappearance of fibrinogen from the blood. P. T. Müller holds that the bone-marrow plays the chief part in the formation of fibrinogen. The old view that it was formed in the intestine was based on faulty experiments. It is possible that the diminution of fibrinogen after injury to the liver is due not to decreased production, but to increased destruction of fibrinogen. Wolf demonstrated that the liver forms substances which hinder fibrinolysis.

Morawitz and Bierich[2] found symptoms of the hemorrhagic diathesis in only 2 out of 3 cases of icterus in which the coagulation time of the blood was much delayed. The old view that delayed coagulation is due to the presence of bile in the blood has been disproved. So far as could be judged from the size and firmness of the fibrin-clot, there was in none of Morawitz's and Bierich's cases any considerable diminution in fibrinogen, nor any noteworthy fibrinolysis. The fact that the blood in a case of cholæmia associated with epistaxis, retinal hemorrhages, and purpura was quickly coagulated by the addition of ten to fifteen drops of tissue extract to 5 cc.

[1] *Bulletin of the Johns Hopkins Hospital*, 1907, xviii, p. 207.
[2] *Arch. f. exp. Path. und Pharm.*, 1907, lvi, p. 115.

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of blood indicated that the delayed coagulation was due to a slow and scanty formation of fibrin ferment or to an inhibition of the action of fibrin ferment. When there is only a small amount of fibrin ferment in blood it may be neutralized by the addition of a little hirudin, the active constituent of the leech, and this gives a rough quantitative test for the amount of ferment present. Tissue extract contains thrombokinase, and Morawitz and Bierich conclude from the experiment referred to above that the reason the blood in this case of cholæmia failed to coagulate was not owing to lack of fibrinogen or fibrin ferment, but to a deficiency of thrombokinase. In phosphorus poisoning, a condition in which the disturbances of hepatic function is marked, thrombin and fibrinogen are diminished in amount.

Diminished coagulability alone does not explain the appearance of purpura and hemorrhage from the mucous membranes. Morawitz and Bierich removed all the fibrinogen from the blood of a dog by repeated bleedings, each followed by an injection of the defibrinated blood. The blood of the dog failed to clot, yet none of the signs of the hemorrhagic diathesis developed.

Microscopic lesions in the liver have been described by Apert, Grenet, and others. They have been observed chiefly in secondary purpuras, and their importance is doubtful. No specific or striking alterations have been discovered. Grenet[1] believes that in cases of purpura in which the liver is healthy the kidneys are often the seat of disease. Experimental studies have indicated that some relation exists between disturbance of hepatic function and purpura.

Changes in the Nervous System.—A type of symptomatic purpura occurring in association with diseases of the nervous system has already been described. Recently cases of purpura have been reported in which there has been a segmental distribution of the purpuric outbreak similar to that in zona.[2] Unfortunately the condition of the ganglia of the posterior roots in none of these cases has been ascertained. Grenet observed a case in which a crop of hepatic vesicles on the face succeeded the purpuric rash. The symmetrical distribution of the eruption so often seen in purpura is regarded as an indication of some relation between the nervous system and the cutaneous outbreak. Lumbar puncture has sometimes shown a distinct meningeal reaction. Lymphocytosis may be marked and considerable albumin present. Two of Grenet's 4 positive cases were in tuberculous subjects. Some observers have reported negative results after lumbar puncture. Cerebral hemorrhage is one of the serious complications of purpura. It is a result rather than a cause of the disease. Henoch says that he who loves hypotheses might ascribe importance to vasomotor influences which produce paralytic dilatation of the smallest vessels and changes in the blood with the result that rupture of the vessels occurs or diapedesis of erythrocytes. Grenet holds that in purpura a toxin exerts a vasodilator action through the nervous system. If the blood is altered by hepatic or other visceral disease, then cutaneous hemorrhages result from the localized vasodilatation.

Bacteriological Studies.—It was held long ago by certain writers that purpura hæmorrhagica was an infectious disease, and a dozen or more investigators have announced that they found bacteria in the blood. Letzerich

[1] *Pathogenie du Purpura*, Thesis, Paris, 1905.
[2] Armand-Delille, *Rev. neurol.*, 1905, xiii, p. 775

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published a detailed description of a spore-bearing bacillus to which the name *Bacillus purpuræ* was given, but his observations have not been confirmed. Recent investigators, working with improved methods, have obtained negative results. Blood cultures were made from several patients of the present series, but no microörganisms were obtained. Litten excised during life bits of skin covered with petechiæ, but could find no microörganisms. Streptococci and *Staphylococcus pyogenes aureus* have been isolated from the blood in cases of symptomatic purpura due to sepsis. Le Count and Batty have described a remarkable case apparently due to a paratyphoid bacillus.

Experimental Purpura.—Koeher and, later, Silbermann produced multiple visceral hemorrhages by injecting blood rich in fibrin ferment into the circulation. Thrombosis and hyaline degeneration of the vessels with associated focal hemorrhage were constant findings in the internal organs, and less regularly in the skin. Silbermann maintained that the primary alteration was in the blood, and that this led to slowing of the blood current, stasis, and thrombus formation. He regarded the changes in the walls of the vessels as the result of thrombosis.

Letzerich and others produced multiple hemorrhages chiefly affecting the viscera by the injection of various bacteria or their products in animals. The experimental conditions bore little resemblance to the clinical or pathological picture of purpura. In Apert's experiments the liver was first injured and then *Bacillus typhosus* injected. Visceral hemorrhages developed, but there were no purpuric spots in the skin. Grenet[1] is the first to produce purpura experimentally unaccompanied by hemorrhages in the viscera. Rabbits were used, and the liver was injured by a temporary ligature of its pedicle. Serum from a hæmophilic patient was injected into the spinal canal. Five days later purpuric spots appeared on the legs. Similar results were obtained when the blood of purpuric rabbits or of purpuric patients was substituted for the hæmophilic blood. Three factors were necessary for the production of purpura: (1) an hepatic lesion, (2) nervous injury, and (3) an intoxication which acted locally on the nervous system. In one case purpura was produced by the intraspinal injection of diphtheria toxin, and he believes that other toxins would give the same result. It is his view that the serum of hæmophilic and purpuric patients contains a toxin which is the active agent in producing the purpura. The hepatic lesion appears in some way to produce changes in the blood which modify the coagulability and produce the hemorrhagic tendency. The role of the toxic action on the nervous system is to provoke bleeding and to determine its location and topography. The purpuric lesions consisted of petechiæ and ecchymoses; erythema was also produced. Grenet maintains that these experiments show the influence of functional disturbances of the liver in the production of purpura.

Pathological Anatomy.—In cases in which death results from hemorrhage the anæmia of the viscera is the most striking and constant finding at autopsy. Petechiæ and ecchymoses in the peritoneum, pleura, pericardium, and endocardium are common. Hypoplasia of the aorta has been described in a few cases (Virchow). Kogerer claimed that thrombi could always be demonstrated, but they were not found in any of the cases examined in the

[1] *Paris Thesis*, 1905.

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pathological laboratories of the Johns Hopkins or Boston City Hospitals. Wagner thinks that the thrombi which do occur have no etiological significance. Many pathologists have examined the bloodvessels of fatal cases with absolutely negative results. The heart is usually fatty. Hoffmann states that the spleen is frequently enlarged. In this series the spleen, liver, and lymph nodes were generally of normal size. In the rare, acute febrile or infectious purpuras the spleen is swollen.[1] Pigmentation from altered blood (Hindelang) and swelling of the lymph nodes have been observed. The lymph vessels and lymph nodes may be filled with blood (Wagner). Hemorrhage into the bone-marrow has been reported (Ponfick). Cerebral hemorrhage has been repeatedly observed and was the cause of death in two cases of this series. Wagner reported a number of cases in which there were hemorrhages into the brain and its membranes similar to those in the skin. In one instance pachymeningitis and a fresh effusion of blood were found. The bleeding is sometimes subdural or subpial. In 5 of Wagner's fatal cases there were numerous fresh hemorrhages in the brain itself. Hemorrhage into the subcutaneous tissues and into the muscles is more apt to occur in purpura hæmorrhagica than in other forms of purpura (Heubner).

Bleeding into the joints in purpura, if it ever occurs, must be excessively rare. Hoffmann says he could not find a definite instance of hemorrhage into a joint in morbus maculosus. In the pathological laboratory of the Johns Hopkins Hospital there is the record of one case in which hæmarthrosis of the left knee-joint was associated with a purpuric eruption over the legs. This may have been a case of scurvy, for there were extensive hemorrhages in the muscles of the right leg, and this is as rare in purpura as it is common in scurvy. The patient, a man aged thirty years, died on the day of admission, before any history could be obtained. Death was due to pneumonia, so that, even if scurvy could be eliminated, the case would have to be classed as a symptomatic, rather than an essential, purpura. Wagner searched the literature up to 1886 without finding a single case of purpura in which a large hemorrhage had occurred into a serous sac—a condition not common in scurvy. No case has been found in the recent literature.

There is a record of only one case of purpura rheumatica that came to autopsy, which was reported by Leuthold from Traube's clinic. There was an œdematous swelling of the capsule of the affected joint and injection of the synovial membrane, with an increase in synovial fluid, which was slightly turbid. The appearance of the joint was said to be quite like that seen in acute rheumatism and in gonorrhœal arthritis.

Small hemorrhages in the mucous membrane of the stomach are very common, but whether they bear any relation to hemorrhage from the stomach is doubtful. Extensive bleeding into the walls of the stomach or intestine is rare. In one case at the Boston City Hospital the wall of nearly the entire small intestine was infiltrated with blood and serum. The diffuse hemorrhage was below the mucosa, and there was no blood in the lumen of the gut. The kidneys are the chief source of blood in hæmaturia, which is a common symptom of purpura hæmorrhagica. The pathological histology of the type of nephritis that so frequently develops during purpura has been studied in but few instances. In one case examined by W. G. MacCallum the kidneys

[1] Gerber, *Wiener klin. Rundschau*, May 14, 1905, p. 329.

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were greatly enlarged, measuring each 12 x 7 cm. There was extensive degeneration in the renal epithelium, but changes in the glomeruli formed the most striking feature. The Malpighian tufts were compressed, by crescentic masses of cells, in the capsular spaces. There was not only a proliferation of the epithelial cells but also a new-growth of connective tissue in the capsules (adhesive glomerulonephritis). In a case of acute nephritis, which terminated with symptoms of the hemorrhagic diathesis, the capsular form of glomerulonephritis was found by the writer. Hemorrhage into the adrenals may occur. Wolff, in a case of only fifteen hours' duration, found the adrenals greatly enlarged, owing to a diffuse hemorrhagic infiltration. Litten observed a case in which there was an adrenal infarct the size of an apple.

All pathologists have agreed with Willan that hemorrhages from the lungs are rare in purpura. They were present in two of this series. In one there was a hemorrhagic infiltration of a lobe and clotted blood in the bronchus; in the other the lungs were studied with hemorrhages. Bleeding into the globe of the eye, producing total blindness, occurred in one case of the present series, and Pepper has reported two cases in which complete destruction of vision in one eye resulted. Small ulcers may develop on the skin, lips, or mucous membrane of the mouth. Gangrene has been observed. In one case sloughing of the anterior two-thirds of the tongue occurred (Fayrer). Musser observed in two instances sloughing of the uvula, and Prentiss gangrene of a portion of the anterior abdominal wall, which was the seat of hemorrhage. Recovery occurred in all of these cases of gangrene.

Symptoms.—Characteristics of the Eruption.—The hemorrhages in the skin usually vary in size from a pinhead to a split pea. Occasionally they are several centimeters in size. Rarely large areas of skin are embraced in a single hemorrhage, or through the confluence of several hemorrhages a considerable extent of surface is involved. The spots are sometimes oval, but usually round. Ring-shaped figures may form (see Plate VIII), but they are very rare. The large patches of hemorrhage often have an irregular contour, giving the skin the appearance of a map. The small spots of hemorrhage are known as *petechiæ*. Dominici[1] designates as petechiæ all purpuric spots less than 10 mm. in size. Lines or streaks of hemorrhage are *vibices*. Larger areas are called *ecchymoses*. The term *suggillation* is applied to an extensive ecchymosis. A fresh eruption is usually bright red, but soon becomes livid or purple. *The color does not disappear on pressure.* Fading occurs within a few days. The colors change from bluish hues to brownish yellow, as they do in ordinary "black and blue" spots resulting from trauma. In a week or so all trace of the eruption disappears, or only a yellowish stain remains. Finally the blood pigment is absorbed, not leaving a trace behind. Successive crops are common, and the spots, of different age and color, give the skin a variegated appearance. The purpuric eruption occurs chiefly on the extremities, particularly the legs, and is often more marked on the extensor surface. The distribution of the eruption in the present series of 194 cases of idiopathic purpura was as follows: legs, 162; arms, 86; body, 64; face, 28. Petechiæ may appear on the tongue, gums, or elsewhere in the mouth. In pure purpura the spots are not elevated about the surface and there is no induration of the underlying tissues. Gangrene is a rare termina-

[1] *La pratique dermatologique*, Paris, 1904, iv, p. 158.

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PLATE VIII

Purpura

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tion. It occurred in only 2 cases in the present series of 258 cases of idiopathic and symptomatic purpura. Another rare complication is the formation of hemorrhagic or clear blebs (pemphigoid bullæ) on the surface of the hemorrhagic spots. According to Bateman, hemorrhagic vesicles are more common on the mucous membrane of the mouth than in the skin. Superficial ulceration of the purpuric spots has been described, and occurred in one of this series. The ulcer was painful and healed slowly. There is an intimate relation between purpura, urticaria, erythema, and angioneurotic œdema. This will be discussed under the clinical varieties of purpura.

The Blood.—As the diminution of the blood platelets and the failure of the clot to contract was thought to have some relation to the origin of the disease, it was described under the heading of pathogenesis. In one of this series, in which there was persistent epistaxis, the blood count on admission was 600,000 erythrocytes per cmm.; leukocytes, 6500; hæmoglobin, 12 per cent.; and the color index 1. Repeated counts of the erythrocytes during the next few days showed that they ranged from 550,000 to 650,000 per cmm. Bleeding from the gums and the stomach occurred later. Before death the red count dropped to "below 500,000." In another patient, a boy aged ten years, diagnosed as purpura hæmorrhagica, the red count fell to 483,000. For two months prior to admission to Dr. Osler's wards he had been languid and losing color. Three weeks before he came to the hospital spontaneous "bruises" appeared on the legs. The purpura was soon followed by the spitting of blood. A blood count was made the day of his entrance, and it was found that there were only 696,000 erythrocytes per cmm., 4000 leukocytes, and 17 per cent. hæmoglobin, and a color index of 0.77. A count made the following morning showed 678,000 erythrocytes per cmm., 6000 leukocytes, and 18 per cent. hæmoglobin. Stained specimens showed no poikilocytosis and moderate differences in size. A differential count of the leukocytes showed 75 per cent. to be small lymphocytes; there were no eosinophiles. One nucleated red blood corpuscle was seen. He died eight days later. The following note by Dr. Thayer is of interest: "While the general condition of the child seemed to improve for a time under careful feeding and iron, the examinations of the blood justified an unfavorable prognosis: (1) In the almost complete absence of regenerative forms (nucleated red corpuscles), (2) in the subnormal number of leukocytes in an acute anæmia, and (3) in the greatly increased percentage of small mononuclear elements."

The clinical course and blood picture in this case are strongly suggestive of aplastic anæmia. Unfortunately the condition of the bone-marrow in these two cases is unknown, as there were no autopsies. In the first case the severity of the anæmia seemed to be out of proportion to the loss of blood. There is apparently a close relationship between aplastic anæmia and purpura hæmorrhagica. The failure of regenerative process in the bone-marrow is the essential feature in aplastic anæmia. Now, the diminished number of platelets in purpura hæmorrhagica probably indicates failure of some regenerative process in the bone-marrow, for the reason that aside from purpura hæmorrhagica great reduction in the number of platelets is seen only in diseases involving the bone-marrow and in which the blood-making function is diminished or disturbed, namely, lymphatic leukæmia and pernicious anæmia. In mild cases of purpura there may be no demonstrable blood change.

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The Color Index.—The fall in hæmoglobin is often much greater than the reduction in red blood corpuscles; Musser and Litten have called attention to this fact. In five of this series the color index was 0.6, and in one instance it was 0.3.

Leukocytosis.—There is often a slight increase in the number of leukocytes above the limit of normal. In two cases of Henoch's purpura the count was 30,000. The leukocyte counts in 59 cases of idiopathic purpura showed from between 3000 to 4000 in 2, 4000 to 5000 in 2, 5000 to 6000 in 2, 6000 to 8000 in 10, 8000 to 10,000 in 8, 10,000 to 12,000 in 13, 12,000 to 15,000 in 9, 15,000 to 20,000 in 6, 20,000 to 25,000 in 4, and 25,000 to 30,000 in 3.

In stained specimens of purpuric blood the number of blood platelets is found greatly diminished in severe cases. The different varieties of leukocytes are present in normal proportions. Microcytes are common.

Lenoble[1] believes he has discovered a new form to which he has given the name of myeloid purpura. This is characterized by the presence of a considerable number of normoblasts in the circulating blood. In the acute stage of the disease the number varied between 165 and 1250 per cmm. In one case he found 3000 per cmm. Sometimes, according to Lenoble, neutrophilic myelocytes and more ralely eosinophilic myelocytes are found in the blood during a myeloid reaction. Labbé and Ameuille[2] conclude from their study that there is nothing specific in the myeloid reaction. It varies with the extent of the hemorrhage and disappears when bleeding ceases. In their case it appeared two days after a severe hemorrhage, and attained its maximum in three days, when six neutrophilic myelocytes and two normoblasts were seen in counting one hundred leukocytes. Five days later, when the anæmia was most intense, there was only a single neutrophilic myelocyte to one hundred leukocytes.

Metabolism.—Magnus-Levy found serious disturbance of metabolism in a case of purpura hæmorrhagica. There was evidence of rapid and extensive destruction of tissue, which he attributed to the loss of blood. Edsall[3] studied the metabolism in case of Henoch's purpura during three periods. The patient was a lad aged sixteen years. During the first period, in addition to extensive cutaneous hemorrhages, there was bleeding from the mouth, nose, stomach, bowels, and bladder. The excretion on the first two days represents total loss, as the patient was taking no food. In fact, he was losing more than the urine analysis indicates, as he was vomiting almost constantly.

Date.	Urine.	Nitrogen.	Uric acid.	P_2O_5.
December 21	1800	22.478	0.192	6.192
" 22	1700	23.738	Lost	4.012
" 23	1350	18.295	0.178	2.484
" 24	870	14.323	0.158	1.531
Return of symptoms, but no hemorrhage:				
December 27	1560	22.579	.....	2.280
" 28	1470	20.580	.....	1.705
Convalescent:				
January 3	880	6.718	.....	0.950
" 4	1275	6.642	.....	0.918

[1] *Arch. de méd. exper. et d'anat. path.*, 1905, xvii, p. 529.
[2] *Bull. et mém. Soc. méd. d'hôp.*, 1905, xxii, p. 1022.
[3] *American Journal of the Medical Sciences*, 1905, cxxx, p. 589.

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During the second period it was impossible to determine the intake, as he vomited frequently. The third set of observations was made when he was gaining weight rapidly and his general condition was good.

The table shows that the nitrogen loss was almost as severe during the second period when there was no hemorrhage as when the bleeding was severe. Edsall calls attention to the low excretion of uric acid, contrasting strikingly with the large amount of nitrogen and P_2O_5 lost. He thinks the P_2O_5 came from nuclein, but that the uric acid produced was destroyed and probably excreted as urea. There is need of more observations on the uric acid and P_2O_5 output in purpura. In leukæmia, on the other hand, the uric acid excretion is generally greatly increased. The studies of Hawk and Gies show that hemorrhage alone does not lead to great tissue destruction.

Clinical Varieties and Symptomatology.—The old view that purpura simplex, purpura rheumatica, and purpura hæmorrhagica are distinct diseases has been largely abandoned. It is necessary, nevertheless, for purposes of study and description to retain these clinical terms until additional knowledge of the nature of idiopathic purpura (morbus maculosus) is acquired. The several varieties exhibit different grades of intensity, but all are characterized by the special feature of hemorrhage either into the skin or from the mucous membranes, or both.

Purpura Simplex.—A purpuric eruption in the skin is usually the only symptom. The purpuric spots are, as a rule, small and the eruption symmetrical on the legs and arms. The legs are the favorite location, but the arms were involved in a considerable number of cases. Spots on the face were noted in four instances. The disease is generally afebrile. Slight fever was noted in only 2 instances among 34 cases of simple purpura. There may be slight pains in the muscles or joints. If the arthritic manifestations are at all marked, the case should be classed as purpura rheumatica, or, better, simple purpura with arthritis. Slight nausea and vomiting may usher in the attack, but the writer cannot agree with Graves that diarrhœa is common in this form of purpura; it occurred in only one case of this series. In 3 cases albumin was present in the urine. Although common in children, in our experience more cases occurred during the fourth decade than at any other period. The duration is stated in text-books to be from one to two weeks, but in our experience it is much longer, the average duration being six weeks, excluding the chronic cases of more than one year's duration. The eruption comes out in crops.

Simple purpura of the chronic type is a well-recognized condition. The duration in 5 of this series was from one to three years. Hayem observed a patient in whom recurring attacks persisted for more than ten years.

Purpura Rheumatica.—This is a bad term for what is nothing more than simple purpura with arthritic manifestations. A still worse designation, because even more misleading, is *Peliosis rheumatica* of Schönlein. Arthritis occurs frequently in association with idiopathic purpura, as was discovered by Johann Schönlein. It is strange that such acute observers as Willan and Bateman overlooked entirely the relation between purpura and arthritis.

The name peliosis rheumatica is doubly objectionable, because it is not a distinct disease, as the word peliosis implies, and the condition is probably not related to rheumatism, as rheumatica indicates. It is important to understand how great was the confusion introduced into the clinical con-

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ception and classification of the different varieties of purpura by Schönlein's description of peliosis rheumatica. Exactly what he embraced under this name is unknown. All the knowledge we have of his views is contained in the notes of his lectures published anonymously "by some of his students." Pagel[1] says that this work was unauthorized and that the notes give a very inaccurate presentation of Schönlein's teaching. In this description the definite statement is made that the spots "*bei'm Drucke des Fingers verschwindend.*" If this be correct, and Schönlein referred to a condition characterized by spots that disappear on pressure, then peliosis rheumatica is an erythema and should not be classed here. Traube, who was closely associated with Schönlein for a period of nineteen years, first as student, later as assistant and colleague, must have been familiar with what the latter diagnosed as peliosis. From Traube's clinic a fatal case of purpura with arthritis was reported under the name of peliosis rheumatica. This would indicate that Schönlein employed this term to designate a purpura rather than an erythema. The following are the characteristic features of peliosis given in the original description: The patients have either previously suffered from rheumatism or at the time of the attack rheumatic pains develop in the joints, particularly the knees and the hands, which become swollen and tender. The erythematous spots appear in the majority of cases, first on the extremities, usually the legs, and only as high as the knees. The spots are small, varying from the size of a lentil to a millet seed, and not raised above the surface. At first bright red, they become dirty brown, then yellowish. There is some desquamation. Repeated outbreaks of the eruption occur often for several weeks, and fever is usually present. The disease differs from morbus maculosus of Werlhof by the absence of hemorrhage, the character of the eruption, the small size of the spots, which never become confluent, blue, or livid, the joint affection, and the lack of nervous symptoms. It is evident that Schönlein described to his students with clearness and exactness the disease picture as he had seen it, but, as Litten points out, it is also evident to anyone who has seen many cases of purpura or who is familiar with the literature of the subject, that Schönlein's clinical experience with the disease was too limited to give any value to this definite clinical picture that he drew. It was later shown by Scheby-Buch that arthritis might occur in purpura hæmorrhagica, *i. e.*, purpura associated with bleeding from the mucous membranes, as well as in purpura unaccompanied by free hemorrhage.

If the term Schönlein's purpura is to be used at all, it should be employed to designate the group of symptoms described. Even during Schönlein's lifetime the term peliosis rheumatica had ceased to have any definite meaning and had become a stone for stumbling in the path of progress. The conception of what constituted the disease underwent various modifications. Fuchs and Hebra said the eruption extended over the entire body. They stated that the joint-symptoms occurred only as prodromal symptoms. Bohm stated that they occurred later in the disease. The vagueness was increased by the publication from Frerich's clinic of a case of ulcerative endocarditis in which hemorrhages from the skin and mucous membranes, as well as the arthritis, were attributed to peliosis rheumatica. In 1860

[1] Article by Schönlein in *Hirsch's Biographisches Lexikon*, Vienna and Leipsic, 1887, v.

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Bamberger published a monograph on nephritis, in which he wrote these words: "The so-called peliosis rheumatica involving the lower extremities is not uncommon in Bright's disease." He then referred in detail to two cases of secondary purpura in nephritis. Instead of applying Schönlein's name to a definite form of hemorrhage—characterized by petechiæ varying in size from a millet seed to a lentil, never confluent, located chiefly on the legs, rarely extending above the knee—it has been employed, as Litten says, to designate every form of cutaneous hemorrhage associated with joint symptoms, including scurvy and erythema nodosum.

The text-books of to-day give descriptions of Schönlein's peliosis rheumatica that vary widely from one another. Strümpell says that in peliosis rheumatica hemorrhages from mucous surfaces sometimes occur. In other words, he would group under this heading any case of purpura associated with arthritis. Osler states that Schönlein's disease "is characterized by multiple arthritis and an eruption which varies greatly in character, sometimes purpuric, more commonly associated with urticaria, or with erythema exudativum." He says that the diagnosis is not difficult, as the association of multiple arthritis with purpura and urticaria is very characteristic.

Under the term simple purpura with arthritis (purpura rheumatica) are grouped all the cases of purpura with arthritic manifestations uncomplicated with hemorrhage from any mucous membrane. In the series of 194 cases of idiopathic purpura, 54 cases fell into this class. This division is convenient for purposes of description, yet doubtless quite artificial, as arthritis of the same type is seen in purpura hæmorrhagica and in Henoch's purpura. Simple purpura with arthritis occurs chiefly between the ages of ten and fifty. It is most often seen in young adults, and is more common in males than in females. A previous history of rheumatism was noted in only 5 cases of this series. The average duration of the entire illness was five weeks, although cases of two weeks' duration were not infrequent. The arthritic symptoms usually persist only a few days, but they frequently recur. As a rule, several joints are affected and the knees and ankles are most commonly involved. There may be swelling or tenderness or pains in the joints, or the three symptoms combined. The swelling is usually slight, and the tenderness and pain are rarely as marked as in typical cases of acute articular rheumatism. The pain may shift from joint to joint. The arthritic symptoms are frequently the first manifestation of the disease, and may be indistinguishable from those seen in rheumatic fever. Within a day or two the purpuric outbreak generally occurs, and with its appearance the arthritic symptoms often subside. Sometimes the joint symptoms and the purpura develop simultaneously. The joint trouble may occur not at onset, but during the course of the disease. It may be transient and be present but once during a long illness. No relation can be traced between the severity of the pain and the amount of swelling. Pain and tenderness may be marked in a joint that is not at all swollen.

The purpuric eruption is similar to that in simple purpura; it is chiefly composed of petechiæ, although patches 3 cm. in size, or even larger, do occur. Cases have been observed in which the eruption appeared chiefly on the affected joints. Heubner cited a case in which the elbows, shoulders, hips, and knees were successively involved. On every affected joint simultaneously with the onset of pain and swelling purpuric spots appeared, and

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with the disappearance of the joint symptoms they faded. Tonsillitis or pharyngitis may precede an attack of purpura arthritica, although in our experience this mode of onset is rare. There is often diffuse pain in the muscles of the arms and legs. The purpuric rash usually recurs several times, and each crop may be associated with pains in the joints. The outbreak may be attended with a sensation of fulness or burning of the extremities. Itching is rare, but may occur without urticaria. In one case in which the eruption recurred repeatedly a sensation of cold preceded each crop of purpura. This prodromal symptom was noted by Willan. There may be malaise at the onset, with slight nausea and loss of appetite. Puffiness of the hands or feet is not uncommon, and there may be great œdema without any evidence of nephritis. In one case of this series there was marked swelling of the legs without nephritis or heart disease. In another the face became so swollen that both eyes were closed; the right forearm and one leg was the seat of a brawny œdema, and the urine was free from albumin. Typical angioneurotic œdema occurred in some cases and purpura arthritica is often associated with urticaria. The combination was noted in nearly 20 per cent. of the series. Erythema is probably more common than statistics indicate, as it is frequently overlooked. It was present in 8 of the series. The usual form is erythema multiforme, although simple erythema or erythema nodosum may occur.

Fever was present in less than half of the cases, and was usually slight and of short duration, but in several instances the temperature rose to 102° and the fever continued for a week or more. In these instances it was generally of the remittent type. Albuminuria occurs less frequently in this condition than in purpura hæmorrhagica. In not a single case in the series did acute endocarditis occur as a complication, and no case has been found reported in this country in which acute endocarditis developed secondary to purpura rheumatica. Pericarditis supervened in a case of purpura recorded by Musser.[1] It was not a typical instance of purpura rheumatica. There was a chronic valvular lesion, and Musser suggested the possibility that the purpura was secondary either to endocarditis or diphtheria. Suppuration of the joints or ankylosis never results. Chronic nephritis is a rare sequel. There is only one fatal case of purpura rheumatica with autopsy on record.

Relation of Rheumatism to Purpura.—Many writers, chiefly English and French, have maintained that purpura rheumatica is a form of acute articular rheumatism. After examining all the evidence it is difficult to see how any one can maintain, in the face of demonstrable facts, that the arthritis of purpura is rheumatic in origin. It is now known that in the past many cases of acute infectious arthritis due to streptococci, pneumococci, and other microörganisms were mistaken for rheumatic arthritis. Cole[2] has clearly shown that streptococcus arthritis may simulate acute articular rheumatism so closely in its clinical aspects that a differential diagnosis is only made by isolating the streptococcus. In some instances of gonorrhœal infection the bacteriological examination alone renders a definite diagnosis possible, as the arthritic symptoms may be identical with those seen in acute articular rheumatism. As long ago as 1886, Wagner insisted that it was sometimes

[1] *Transactions of the Association of American Physicians*, 1891, vi, p. 279.
[2] *New York Medical Journal*, March 17, 1906.

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impossible even after prolonged observation to decide definitely whether one is dealing with a case of true rheumatism or not. Diagnosis is only possible through a knowledge of the history and a study of the accompanying phenomena.

The following facts indicate that the arthritis of purpura is not due to rheumatism:

1. Pains and swelling in the joints may occur in association with effusions of blood in other parts of the body. Among Dr. Osler's records there are notes of two cases, in one of which the arthritis was in connection with hemorrhage into a pancreatic cyst; in the other a protracted arthritis followed a fall on the back, with resulting hæmaturia from laceration of the kidney.

2. In arthritic purpura a history of a previous attack of rheumatism is rare. It was elicited in only 5 out of 54 cases of purpura rheumatica. The joint symptoms are usually transient and the pain not severe. Fever is absent in one-half the cases, and when present is rarely high. Hyperpyrexia was not observed in any of this series, and in only one was there profuse sweating. Endocarditis did not occur in any of this series. The pain in purpura arthritica, unlike that in rheumatism, is rarely relieved by salicylates.

3. If the so-called purpura rheumatica is a manifestation of rheumatism, why does purpura occur so rarely in typical febrile cases of acute articular rheumatism? This question, which Scheby-Buch raised over thirty years ago, has never been satisfactorily answered. In a search of the literature he failed to find a single case of purpura in which the typical picture of rheumatic fever was present. In a study of the records of 4000 cases of acute articular rheumatism he found only a single case in which it seemed quite probable that purpura was associated with true rheumatism, but even this may have been tuberculous arthritis. Undoubtedly symptomatic purpura may occur in rheumatism as in all other infectious diseases, but it is rare. In the records of the Massachusetts General Hospital, since 1874, there are only 4 cases of purpura in which it seemed at all probable that the disease was rheumatic in origin. At the Johns Hopkins Hospital, for the fifteen years ending in 1904, there were 330 cases of rheumatic fever (McCrae), and there was not a single case of purpura in this entire number.

Purpura and Urticaria.—This association is frequent. Urticaria may occur in all forms of purpura, but it is most frequently seen in simple purpura with arthritis (purpura rheumatica) and in Henoch's purpura. It was noted in 11 of the 54 cases of purpura rheumatica in this series, and doubtless occurred in a mild form in many more cases than were recorded. Dr. Osler, who has been much interested in the relation of urticaria to purpura, reported the presence of urticaria in 17 out of 29 cases of "the erythema group with visceral lesions." Four types of eruption are seen: (1) The purpuric spots may be slightly elevated (purpura papulosa). This is the simplest form of purpura urticans. (2) Hemorrhage into definite urticarial wheals. (3) Simultaneous outbreak of purpura and urticaria. Purpura urticans includes these three types. (4) A purpuric attack may be followed by an urticarial eruption, or the reverse may occur. Osler reported a case in which, after outbreaks of urticaria for years, the final symptoms were those of a severe purpura hæmorrhagica.

Sometimes the combination of purpura and urticaria gives the skin a remarkable appearance, as in a patient aged sixteen years, who was convalescing from an attack of simple purpura. On December 8, 1905, in the

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morning only fading petechiæ were present, but at 5 P.M., over both lower legs, but chiefly on the outer side of each, a great number of wheals 5 to 7 mm. in size were present, so thickly set as to present the appearance of a coarsely grained leather or a pebbled surface. The color of the elevations was reddish and did not disappear on pressure. The infiltration of the skin of the affected area was marked. Scattered between the wheals were a number of fresh, bright red petechiæ the size of a pin's head and not elevated above the surface. Above the knees were scattered wheals and petechiæ, but none elsewhere on the body. There was no itching. On the next day, at 1 P.M., there was no trace of urticaria or infiltration of the skin remaining, and the sites of the wheals were represented by rose-colored petechiæ. The patient was unconscious of this outbreak of purpura, and the pulse and temperature were uninfluenced. He had no joint pains or digestive disturbances.

In one case (see Plate VIII) purpura urticans of unusual type recurred repeatedly during a period of two years. Colorless, circular nodules first appear and become hemorrhagic. The areas extend peripherally, forming larger and larger circles; the advancing border is always indurated.

In purpura urticans itching may occur, but it is usually absent. On the other hand, itching may accompany a purpuric outbreak when no urticarial lesions develop.

Between urticaria and typical erythema transition forms exist which in local and general manifestations offer diagnostic difficulties (Wagner). Under the term urticaria are embraced those cutaneous exudations characterized by rapidity in developing and disappearing and the absence of desquamation. Sometimes erythema nodules become so filled with blood that they resemble a hæmatoma of traumatic origin. This condition is sometimes designated as purpura urticans, or urticaria hæmorrhagica.

Purpura and Erythema.—Thibierge and other French writers group under the erythemas both the purpuras and the urticarias. The exudative erythema, according to Wagner, includes at least three different forms: (1) urticaria; (2) erythema exudativum multiforme; (3) erythema nodosum. Most authors do not include urticaria. Osler regards purpura rheumatica as the hemorrhagic type of an exudative erythema, and he would place Henoch's purpura in the same group. He has clearly demonstrated in a series of papers "the close affinity that exists between exudative erythema, Henoch's purpura, peliosis rheumatica, and angioneurotic œdema. This is shown by (1) the similarity of conditions under which they occur, (2) the identity of the visceral manifestations, and (3) the substitution of these affections for each other in one and the same patient at different times. The student is, however, at the outset confronted by this interesting feature. On the one hand similarity of lesions may result from a variety of causes. The purpuric rash of iodism, of endocarditis, of scurvy, and of smallpox is identical. The wheals of urticaria from nettles, of an acute gastric toxæmia, and from the poison of the malarial parasites are indistinguishable. A typical exudative erythema may result from several causes. On the other hand, unity of cause may be associated with a variety of lesions. . . . We cannot say why in one case there is exudate of red blood corpuscles without erythema (purpura), in another a serous exudate with hyperæmia (urticaria), in a third serous exudate with hyperæmia and hemorrhage in varying degrees

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(erythema exudativum multiforme), in a fourth serous exudate alone (localized œdema). Two or three of these lesions may co-exist or may rapidly succeed each other during the same attack, or in succeeding attacks the skin lesions may vary, urticaria in one, purpura in another, and so on" (Osler[1]). He points out, furthermore, that this great variability in character of the skin lesions is of importance, as it is quite possible that within a year in an individual patient the diagnosis might be given of simple purpura, peliosis rheumatica, angioneurotic œdema, exudative erythema, and simple urticaria.

Osler places all these conditions together in what he terms the erythema group. He has studied a series of 29 cases in which there were polymorphous visceral lesions, of which the most prominent were crises of abdominal pain and hemorrhages. Henoch's purpura belongs in this class. In 22 of the 29 cases there was purpura, in 17 urticaria, and in 14 erythema. The name is not entirely satisfactory for this group. It is, in fact, somewhat misleading and confusing, as the pure type of erythema was present in only half the cases, and in a less number than urticaria or purpura.

E. Wagner[2] wrote a valuable monograph on purpura and erythema. In a space of nine years he saw 19 cases in which there was a combination of erythema and purpura associated with acute joint manifestations; 10 of the cases were mild and 9 severe. The character of the erythema varied, but the most common form was erythema nodosum. The nodules after a shorter or longer time usually became hemorrhagic, and sometimes small hemorrhagic vesicles formed. The gastro-intestinal complications which were such a striking feature in Osler's cases of combined erythema and purpura were almost lacking in Wagner's series.

Erythema and purpura have many features in common. Both are rare, both affect chiefly young individuals, and they may occur simultaneously in the same individual. Prodromata of both diseases are often the same—general malaise, gastro-intestinal symptoms, pain in the limbs, and fever. In both affections arthritis of the same type and hemorrhages from the mucous membranes occur, and in both severe crises of abdominal pain may be present.

This similarity of purpura rheumatica and erythema exudativum is well shown in the following case, seen with Dr. Bucher at the Naval Hospital in Chelsea: The patient never had rheumatism, and complained of general muscular and joint pains, specially marked in the elbows, wrists, knees, and ankles. His temperature was then 100°. The fauces were very red. An erythematous eruption was present on both hands and feet. During the next two days the fever ranged from 101° to 102°. He had slight epistaxis, headache, nausea, vomiting, and sweating. The urine contained a trace of albumin. Three days later the joint pains had disappeared; there was a fading erythematous rash on hands and feet, with no infiltration of the underlying tissues, and in the left upper eyelid an ecchymosis 1 to 2 cm. in size. There was no swelling of the joints and no albumin in the urine. An interesting feature was the simultaneous outbreak of a marked eruption of erythema and one purpuric spot.

Endocarditis, rare in purpura, is common in erythema exudativum. In

[1] *Jacobi's Festschrift*, New York, 1900, p. 459.
[2] *Deutsches Archiv f. klin. Med.*, 1886, xxxix, p. 431.

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Lewin's collection of 126 cases endocarditis developed in 27. In 64 cases of his series arthritis existed.

The arthritis of erythema, like that of purpura, has frequently been regarded as rheumatic in origin, notwithstanding the great rarity of erythema in typical cases of rheumatic fever. Pye-Smith found only 2 cases of erythema among 400 of rheumatic fever. Lewin concluded after careful study that there was no evidence that there was any connection between erythema and rheumatism.

In this series of 194 cases of idiopathic purpura there were 20 with erythema. The tenderness so characteristic of erythema nodosum has been seen in purpura unassociated with any induration of the tissues.

Erythema Nodosum (Synonyms: Dermatitis contusiformis; urticaria tuberculosa).—Many of the older writers grouped this form of erythema, particularly the cases in which arthritis occurred, with purpura rheumatica (Canstatt, Bohn). There is an atypical type of nodular erythema not painful to pressure occurring chiefly on the forearms. This is sometimes regarded as an unusual form of erythema nodosum, but is perhaps more properly classed as a variety of purpura urticans.

Anatomically erythema exudativum and erythema nodosum are similar. Both consist of exudations into the cutis which are frequently, if not constantly, hemorrhagic.

Purpura and Angioneurotic Œdema.—In 49 of the 194 cases of idiopathic purpura œdema was present, and in 6 instances typical angioneurotic œdema occurred, and many of the other cases were probably of the same nature, as œdema was transitory and often localized on the hands and face. Osler attributes the colic of Henoch's purpura to localized œdema of the intestinal wall. Definite colic occurred in 34 of this series. The sudden swelling of the hands and feet so frequently seen in purpura is probably related to angioneurotic œdema. As Osler has pointed out, there is really no warrant for separating angioneurotic œdema and urticaria too sharply. In two cases angioneurotic œdema, purpura urticans, and ordinary purpura occurred together. Oppenheimer has seen angioneurotic œdema and urticaria develop simultaneously. The intimate relation of purpura and angioneurotic œdema is shown in the case of a man aged fifty-five years who, during six weeks had "about two dozen" attacks of purpura of the legs, associated with transitory localized œdema of the legs. The swelling of the legs was so great in the first attack that his trousers had to be cut in order to remove them. The œdema developed with great rapidity, red spots being first noticed, and within five or ten minutes the swelling began. The last attack was accompanied by severe pain in the epigastrium and vomiting. On examination there was no œdema, but both legs were nearly encircled above the ankles by a band of discrete and confluent spots of dingy brick-red color, which did not disappear on pressure.

The Angioneurotic Group.—All these closely allied conditions—Henoch's purpura, erythema, urticaria, and localized œdema—are probably manifestations of an angioneurosis, and it would be well to group them, at least tentatively, under this name. Localized vascular dilatation or exudation (serous or hemorrhagic) occurs in every case, and the claim of an angioneurotic origin has already been made for each member of the group. The elder Romberg, Barensprung, and particularly Lewin regarded erythema exudativum as an angioneurotic dermatosis, and this view is held by the most

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recent writers.[1] The angioneurotic dermatoses are characterized by a marked disturbance of the vascular tonus, in addition to a more or less pronounced inflammatory condition of the skin. They are due to an abnormal tendency of the skin to react to slight and varied irritants with the production of inflammatory changes (dilatation of the vessels and exudation), which must be regarded as constituting a distinct disease. This sensitiveness of the skin and the abnormal reaction is the result of a general angioneurotic disturbance. These dermatoses must be distinguished from the simple cutaneous inflammations which result from the action of inflammatory irritants upon normal skin (Auspitz). They include urticaria as well as the erythemas, and may result from the action of different toxins on the nerve centres (Caspary).

Osler[2] in 1888 advanced the theory that the entire group may depend upon some poison "which in varying doses in different constitutions excites in one urticaria, in a second peliosis rheumatica, and in a third a fatal form of purpura." Klippel et Lhermette[3] voiced the same opinion recently when they asserted that no sharp barrier can be set up between certain forms of purpura and erythema exudativum multiforme. "It is a question of virulence of the infectious agent and of variation in the resistance." Acute localized œdema is generally regarded as an angioneurosis, as the name angioneurotic œdema indicates, and the same is true of dermatographia and factitious urticaria. In Henoch's purpura the view is widely accepted that the abdominal colic is due to angioneurotic œdema of the intestine, and there is strong evidence for grouping all these conditions under the name angioneurosis.

Henoch's Purpura, or Purpura Abdominalis.—This form of purpura is characterized by recurrent attacks of purpura and crises of abdominal pain, often accompanied by vomiting and diarrhœa. The stools and the vomitus may contain blood. Arthritis is present in the typical form of the disease, and nephritis is a serious and very common complication. The relation of Henoch's purpura to other members of the angioneurotic group has been discussed on a previous page. Osler has shown that similar abdominal manifestations occur in erythema and urticaria. Henoch first observed this type of purpura in 1868, and six years later published a report of 4 cases.[4] Abdominal pain and even severe colic had been occasionally noted in cases of purpura since the time of Willan, but Henoch was the first to study them with care and to show their connection with the hemorrhagic process. The gastro-intestinal disturbances had previously been attributed to splenitis or to congestion of the liver.

It is a disease of early life, as shown in this series: One to 10 years, 11; 10 to 20 years, 19; 20 to 30 years, 6; 30 to 40 years, 3; and 40 to 50 years, 4. The youngest patient was four years and the eldest forty-seven years of age. Cases in children three years old have been reported (Olliviers d'Angers, Handfield Jones). In one of this series typical attacks of colic with arthritis began at the age of two years, but the patient did not come under observation until five years later, when purpura was present. It may have occurred

[1] Caspary, *Die deutsche Klinik*, Berlin and Vienna, 1905, x, p. 91. Gérome, *Zeitschrift für klin. Med.*, 1906, lx, p. 383.
[2] *New York Medical Journal*, December 22, 1888.
[3] *Archives générales de Médecine*, 1904.
[4] *Berliner klinische Wochenschrift*, 1874, Nr. 51.

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during previous attacks and have been overlooked by the parents. The disease is more common in males than in females. In a series of 40 cases collected from the literature by v. Dusch and Hoche,[1] 33 were in males and 7 in females. Of our 43 patients, 31 were males and 12 females.

General Features.—The onset varies. Sometimes there is headache, anorexia, and prostration, or the purpuric outbreak or abdominal colic ushers in an attack. The patients complain of severe pain in one or more joints, similar in character to that in other varieties of purpura. Fever is usually absent, and when it occurs it is generally slight and of short duration. The appearance of the purpuric spots is often unnoticed by the patients, especially when confined to the legs and unattended with any subjective sensation, such as burning, tension of the skin, or itching. The arthritis often precedes the purpuric rash by a period of several days. Soon the abdominal symptoms appear and dominate the scene. The pain is colicky in character, often agonizing, and forms the most distressing feature of the attack. It does not yield readily to treatment, and sometimes continues for days. At the onset of pain the abdominal wall is usually rigid and contracted and there is diffuse tenderness. At first the bowels are constipated, and if they do not move for several days the mistaken diagnosis of acute intestinal obstruction may be made. Often the initial constipation is followed by diarrhœa. Vomiting frequently adds to the distress of the patient; the vomitus, which at first consists of food, is later admixed with bile, and sometimes with blood. The pulse is small and frequent. After a few days the gastro-intestinal symptoms cease, the purpuric spots fade, the arthritis disappears, and convalescence seems established. The duration of a single attack may not be more than one or two days. The symptoms rarely persist for more than a week. The average duration of the entire illness in our series was one month.

Rarely does the disease consist in a single attack, for in the vast majority, after an interval varying from a few days to weeks or months, another attack occurs. Couty reported a case in which the symptom complex recurred nineteen times, but four or five recurrences are the rule. In a patient observed at the Johns Hopkins Hospital there must have been over sixty attacks; for over a period of five years typical gastro-intestinal seizures occurred with intervals of less than a month. It is the composite picture of the disease that has been sketched above. The individual cases present many variations. Henoch realized this, for he points out in his text-book that "single rings in the chain of symptoms may be lacking."

The occurrence of erythema and urticaria in association with Henoch's purpura has already been considered. Urticaria was present in 13 cases (30 per cent.) and erythema in 6. Œdema developed in 15 cases. Puffiness of the backs of the hands and swelling of the feet are common. In several instances typical acute angioneurotic œdema occurred. Not only has Osler shown the variability of the skin lesions, but he has reported cases in which in some of the attacks agonizing colic occurred without any cutaneous eruption. In 39 of this series there were purpuric spots on the legs, in 22 on the arms, in 14 on the body, and in only 4 on the face. The patients frequently locate the pain in the region of the umbilicus, a fact which Dusch and Hoche comment upon. In a considerable number the pain is in

[1] *Pädiatrische Arbeiten. Henoch's Festschrift*, Berlin, 1890.

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the epigastrium or the lower abdomen. Henoch states that in his cases there was always tenderness in the upper part of the abdomen. In 36 of the 43 clinical records the definite statement was made that the pain was colicky in character. Sometimes it shifts from one part of the abdomen to another. Colic may be the only symptom; more frequently there is also vomiting or diarrhœa. In this series vomiting occurred 31 times and diarrhœa 12 times. The passage of blood in the stools is more frequent than vomiting of blood. The former symptom was present 15 times and the latter only 6 times. The abdomen is sometimes distended; in one patient distinct waves of peristalsis were seen. Arthritic pains were present in all but 5 of the 44 cases analyzed by v. Dusch and Hoche, while among this series of 43 cases they were noted in 27 of the clinical records. The knees and ankles were the joints most frequently involved. Epistaxis is not uncommon, and occurred in 8 of this series, while bleeding of the gums was noted in three instances.

Fever was present in one-third of the cases, but a temperature above 101° is rare. The spleen was not often palpable in this series, but it has been found enlarged by other observers in quite a number of instances. There is usually a slight leukocytosis. Blood counts were made in 16 cases, and in 2 a leukocytosis of 30,000 was recorded, but usually the number of leukocytes is below 14,000.

The most serious complication is acute nephritis, and in no other variety of purpura is it as common, being present in no less than 20 of 43 cases. It was frequently of the acute hemorrhagic type. There is usually a considerable amount of albumin and numerous tube casts. Œdema may be absent even in a case of intense nephritis (Osler). Hæmaturia occurred in 4 cases of this series, and it has been shown that in this disease the kidney is the usual source of the blood in the urine. One of the two fatal cases in this series resulted from nephritis. Cerebral hemorrhage, endocarditis, pericarditis, and pleuritis are rare complications. Intussusception occurred in one case (Sutherland).

The prognosis is better in children than in adults. Among 102 cases of Henoch's purpura (the present series combined with that of v. Dusch and Hoche, and cases collected by Macalister[1] from the records of Guy's Hospital), 8 resulted fatally. One of our series died of cerebral hemorrhage at the age of sixteen after repeated attacks during a period of seven years. Motor aphasia developed suddenly, and when brought to the hospital she could not speak and the right arm was weak; convulsions developed later. An exploratory operation was performed, and the brain and subpial space were of a uniform cherry-red color. There was no possibility of doing anything and death occurred four days later.

The cause of the gastro-intestinal symptoms is unknown. Scheby-Buch thought the colic might be due to hemorrhages in the serosa of the intestine. This explanation did not satisfy himself, however, and he called attention to the rarity in other diseases of the association of colic with intestinal hemorrhage. In a case that occurred recently at the Boston City Hospital there was no colic, although the autopsy revealed extensive hemorrhage and serous exudation into the wall of the small intestine. Sutherland[2] has

[1] *Guy's Hospital Gazette*, 1906, xx, p. 176.
[2] *British Journal of Children's Diseases*, 1904, vol. i, No. 1.

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reported a case in which localized hemorrhage beneath the serosa and thickening of the wall of the bowel were found at operation. In many of this series severe colic occurred unaccompanied by bleeding from the stomach or bowels. As has been stated, similar abdominal manifestations may develop in other members of the angioneurotic group, and Osler[1] has reported a case of generalized telangiectasis with similar attacks of colic.

Osler thinks that the pain in the abdomen is associated with a localized urticarial swelling of the gastro-intestinal wall. In fact, this condition has actually been found at operation made during an attack of colic (F. B. Harrington).[2] The studies of Lennander[3] indicate that either serous or hemorrhagic infiltration of the wall of the stomach or intestine, if sufficient to produce stretching of the parietal (mesenteric) attachments, would produce colic.

The Surgical Importance of the Recognition of the Visceral Crises.—The literature shows that at least six patients have been subjected to an exploratory laparotomy during the past few years for this form of colic. The practical lessons to be drawn from this experience are: "First, that in children with colic the greatest care should be taken to get a full history, which may bring out the fact of previous attacks, either of skin lesions, of arthritis, or of intestinal crises; and secondly, to make the most careful inspection of the skin for angioneurotic œdema, purpura, or erythema" (Osler).[4]

Thousands of attacks of severe colic occurred among the cases of Henoch's disease that have been reported. With the exception of one case, in which intussusception was found at autopsy, recovery from the colic has occurred in every instance.

Purpura Hæmorrhagica.—Hemorrhages from the mucous membrane is the feature that distinguishes this type of the disease from purpura simplex. Most of the serious cases of purpura are embraced in this variety. The onset is usually abrupt, the initial symptoms often severe. In some instances the bleeding from the mucous membranes is slight. The cutaneous hemorrhages in purpura hæmorrhagica are usually more extensive, and the body and face are more frequently involved than in purpura simplex. Large ecchymoses may cover the limbs and trunk. The skin may look as if it had been spattered with a paint-brush. In some cases slight pressure on the skin produces an extravasation of blood. All authors are agreed that epistaxis is the most frequent form of hemorrhage in this disease. In this collection of 48 cases of purpura hæmorrhagica bleeding, from the nose occurred in 24 (50 per cent.). The gums were the seat of hemorrhage in 20 cases, while in 7 cases the blood came from other parts of the mouth. In Wagner's experience hemorrhage from the urinary organs was more common than from the mouth. In this series hæmaturia was present only five times. Bleeding may occur from other places—intestines, stomach, uterus, and rarely the lungs. In this list the cases of Henoch's purpura have not been included, although classed by some writers as purpura hæmorrhagica. The rarity of erythema and urticaria in the latter indicates a difference in the two conditions.

[1] *Bulletin of the Johns Hopkins Hospital*, October, 1907.
[2] *Boston Medical and Surgical Journal*, March 30, 1905.
[3] *Journal of the American Medical Association*, September 7, 1907.
[4] *American Journal of the Medical Sciences*, May, 1904.

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The duration of purpura hæmorrhagica is usually longer than purpura simplex or the so-called purpura rheumatica. A few of our cases lasted only one to two weeks, but the average duration was two months. There is a chronic form which may persist for many years. A case of this type referred to under chronic purpura lasted more than thirty-six years.

French writers separate the febrile and the afebrile cases. The latter are grouped under the heading purpura hæmorrhagica of Werlhof, while the former are regarded as infectious in nature and are placed in a class by themselves. Some would even subdivide them into typhoid and septic types. Many of the cases of so-called infectious purpura are doubtless symptomatic purpura in which the primary disease, *e. g.*, ulcerative endocarditis, has been overlooked.

Fever was present in 25 of our 48 cases, but was usually mild, the maximum temperature being 103°. According to Kernig, continuous subfebrile temperature (99.5° to 100°) is not uncommon. If hemorrhage is severe, collapse with subnormal temperature may be present. Sometimes the spleen is swollen. The liver may be enlarged and painful, but this is rare. Slight icterus is not infrequent, according to Laache and Litten, but was not observed in any of this series.

Arthritis is common, although, singularly enough, the association of joint symptoms with purpura hæmorrhagica was not known until Scheby-Buch published his monograph in 1874. He showed that the same type of arthritis existed in purpura hæmorrhagica as in purpura simplex. In his series there were 20 cases of purpura simplex without and 18 with arthritis; 9 cases of purpura hæmor hagica with and 26 without joint symptoms. Rheumatoid pains of the joints and muscles occurred in 16 of our 48 cases of purpura hæmorrhagica. Œdema was present in no less than 10 cases, the feet and legs being most commonly affected, but sometimes the hands, arms, or face. Vomiting is common, but diarrhœa is rare. Acute nephritis is the most important complication, owing to its frequency and its severity, and is usually of the hemorrhagic type. It is not as common, however, in this variety of purpura as in Henoch's disease. Owing to the greater loss of blood, anæmia is more marked than in the other purpuric conditions. Hæmatorrachis and hæmatomyelia have been described, but are excessively rare complications. Swelling of the testicle with hemorrhage into its substance has been noted by Eichhorst.

Purpura Fulminans.—In this very rare variety ecchymoses extend with startling rapidity, and within a few hours an entire extremity or the greater part of the trunk may assume a blue or reddish-black color. This disease usually ends fatally in from eighteen to forty-eight hours, and no patient has recovered. Guelliot, in 1884, was the first to describe this condition, which was more carefully studied by Henoch,[1] who gave the name purpura fulminans. There is no hemorrhage from the mucous membranes, and hence it comes under the heading of simple purpura. There is a certain irony in applying the term simple purpura to a disease that is one of the most surely and rapidly fatal of which we have knowledge.

Stybr could find only 13 cases in the literature up to 1906. Risel,[2] in 1905, analyzed 12 cases, but he did not include 5 American cases that

[1] *Berliner klinische Wochenschrift*, 1887, p. 8.
[2] *Zeitschrift für klinische Medizin*, 1905, lviii, p. 163.

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had been reported. All the typical cases have been in children, and the youngest was in an infant aged two months (Stybr). Three occurred during convalescence from scarlet fever. Bacteriological examinations were negative except in one case reported by Borgen, in which streptococci were found in the blood. This and one reported by Litten, of rapidly fatal purpura associated with streptococcus septicæmia, should be placed among the secondary purpuras. Heubner is possibly right when he classes this type of purpura with the septic diseases. Litten and Nehrkorn have reported cases similar to purpura fulminans, but with much bleeding from the mucous membranes.

The duration has been from ten hours to five days, and all undoubted cases have been fatal. Hemorrhagic bullæ formed on the skin in 2 cases. Grozs and Goerges have reported cases in which recovery occurred, but Risel thinks they were dealing with erythema exudativum multiforme. Death from cerebral hemorrhage occurring in the beginning of an attack of purpura may lead to the mistake of diagnosing the case one of purpura fulminans. From a study of the literature it is apparent that some observers have fallen into this error.

The only case in this series exhibiting a fulminating character was doubtless an example of some general infection.[1] The patient was a vigorous young man aged twenty-one years, who on December 21 was in his usual health. In the evening he carried a heavy trunk down stairs, and about 11 o'clock that night he began to feel sick and vomited. At 8 o'clock the next morning W. D. Swan examined him and found his temperature to be 102°. He complained of severe backache and had other symptoms suggestive of influenza, but during the forenoon a purpuric eruption appeared on the face, and he died at 3.30 P.M. The entire duration of the illness was less than seventeen hours. Dr. Councilman made the autopsy. The face was thickly covered with purple spots and blotches, ring-shaped, varying in size from a pinhead to a bean. Similar spots were present over the shoulders and trunk, and in less number on the arms and legs. There were hemorrhagic spots in the subcutaneous tissues and on various serous membranes. There was acute congestion and œdema of the lungs. Cultures made from the kidney and lungs showed streptococcus and staphylococcus aureus in considerable number. The most extraordinary feature was revealed on the histological examination. Careful search failed to reveal a single normal polynuclear leukocyte in the tissues. Only a few polynuclear leukocytes were seen, and these were degenerated and their nuclei fragmented.

Chronic Purpura.—There are two forms of chronic purpura. In one the hemorrhages into the skin or from the mucous membranes continue uninterruptedly for years, while the other type is characterized by recurrent attacks separated by intervals of health. Wagner held that the disease occurred chiefly in childhood among the weak and anæmic. He cites the case of a child aged five years who, every three or four days, during a period of three years, would be attacked by fresh hemorrhages; sometimes petechiæ or large ecchymoses would appear, and sometimes there would be vomiting of bloody mucus or the passage of urine or fæces mixed with blood. The patient

[1] Dr. J. H. McCollom has seen an exactly similar case in a house epidemic of scarlet fever. He suggested to the writer the possibility that this was a case of scarlet fever.

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recovered entirely. It is interesting to note that a paternal uncle died of acute purpura hæmorrhagica.

Bensaude and Rivet[1] state that the continuous form of chronic purpura is the rarer. Subjects of this disease usually consult a physician on account of weakness or for some gastro-intestinal disturbance. On examination purpuric spots are found. In these individuals epistaxis and bleeding from the gums are common, but severe hemorrhages are rarely observed.

In the intermittent form the recurrence is usually preceded by frequent hemorrhage from a single mucous membrane, especially from the nose or mouth. The duration of this affection is variable. Attacks are said to have occurred over a period of more than twenty years. Bensaude and Rivet have observed 14 cases of chronic purpura hæmorrhagica and collected 20 others from the literature. In one of their cases there was an interval of seven years between the second and third attacks. Mistakes in diagnosis have been common; when the hemorrhage has occurred from a single organ it has frequently been mistaken for a local disease. When the hemorrhages are multiple or follow slight trauma, this condition is frequently confused with hæmophilia, but the two affections are quite distinct. Hæmophilia is congenital and hereditary, and, although the blood shows considerable diminution in coagulability, the clot, once formed, contracts, as Hayem has shown, in a normal manner. In chronic purpura hæmorrhagica, on the other hand, the coagulation time is normal, but the clot remains absolutely non-contractile. The platelets are diminished. Bensaude and Rivet believe that the presence of these two characteristics of the blood will permit the diagnosis of chronic purpura even in the absence of a purpuric eruption. The prognosis in chronic purpura should be made with reserve. In view of the long latent periods, it is impossible to assert in any case that the disease has been cured. The mortality is high, according to Bensaude and Rivet; five of their patients died during attacks.

In this series are 20 cases of purpura in which the disease persisted for a year or more. This list includes simple purpuras with and without arthritis, purpura hæmorrhagica, and Henoch's disease. The longest duration was thirty-six years, in a patient under Dr. Osler's observation for some time. She had had frequent recurring epistaxis with occasional crops of purpura since her tenth year. Only one of our chronic purpuras resulted fatally. Death in this case was due to cerebral hemorrhage. In 1898, Dr. Halsted operated on a woman for carcinoma of the breast who had had recurring attacks of purpura almost from childhood. There was no special bleeding at operation, and she made a good recovery.

Some cases of chronic purpura show a marked tendency to hemorrhage, as in a patient seen with J. W. Coe[2] in New York. The patient was at that time seventeen years old and had had recurrent attacks of severe epistaxis for twelve years, often accompanied by a purpuric eruption. At the age of thirteen, after having a tooth pulled, he bled profusely for three hours. The family history was negative. Examination of the blood showed the platelets to be greatly diminished in number, with the coagulation time normal.

[1] *Arch. gén. de méd.*, 1905, i, p. 193, 272.
[2] Reported in the *Journal of the American Medical Association*, 1906, xlvii, 1090.

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Purpura Hæmorrhagica without Skin Symptoms.—There are some cases of the hemorrhagic diathesis which present the clinical picture of purpura hæmorrhagica, except that cutaneous hemorrhages are absent. There is no hereditary or congenital tendency to hemorrhage, and hence they cannot be classed under hæmophilia. In some chronic cases of this type the diagnosis is confirmed subsequently by the appearance of purpuric spots in the skin. Osler[1] has reported such a case with recurring abdominal crises and bleeding at the nose for a year, before a purpuric rash appeared during an attack.

J. W. Coe studied a patient in whom, during a period of twenty-eight years, there had been frequent attacks of epistaxis so severe that packing of the nostrils was often necessary. There was no history of bleeders in the family, and he had never had arthritis. The blood showed a greatly diminished number of platelets (22,000 per cmm.), and the coagulation time was not definitely retarded. Hayem claims that a marked reduction in platelets does not occur in hæmophilia. Owen observed a case of this type in a girl aged eleven, who had hemorrhages for twelve months, first from the bowels, then from the nostrils, and afterward from the left ear. There was no history of bleeders in her family, no arthritis, and no purpura.

Diagnosis.—The Symptom.—Flea bites may closely simulate true petechiæ. Henoch says that in examining children on their admission to the hospital he has often been in doubt whether the hemorrhagic spots present were due to flea bites or to the hemorrhagic diathesis. Flea bites are quite small and usually show a central point which is the result of trauma.

Telangiectatic spots may be mistaken for purpura at the time of the first examination of a patient. Petechiæ quickly fade and disappear, while telangiectatic spots remain indefinitely. Furthermore, on palpation of the latter the color usually disappears momentarily or is replaced by a brownish stain. A case of generalized telangiectasis was admitted to the hospital with abdominal colic. He was tossing about the bed in agony, and it was impossible to obtain a satisfactory history owing to his condition. The telangiectatic spots were mistaken for petechiæ, and in view of the fact that he was passing bloody urine and suffering from colic, the disease was regarded as Henoch's purpura. Occasionally telangiectasis associated with recurrent hemorrhages from the mucous membranes is mistaken for chronic purpura.

Erythema exudativum multiforme is sometimes diagnosed as purpura. Physicians as well as students forget that if the color disappears on pressure the lesion is erythematous and not purpuric. It is well to use an ordinary glass microscopic slide for making this test.

The Disease.—There is danger of mistaking infectious diseases with hemorrhagic manifestations for idiopathic purpura. At the onset of a case of purpura with fever this possibility should be borne in mind. Without doubt many cases of acute lymphatic leukæmia with symptomatic purpura have been mistaken for purpura hæmorrhagica. The symptoms and clinical course of the rapidly fatal cases of leukæmia, with little or no enlargement of the lymph nodes, may be indistinguishable from the morbus maculosus of Werlhof. *An examination of the blood should be made in every case of purpura.* If this is done leukæmia can usually be definitely excluded. Hastings[2] has reported a fatal case in which the blood picture, as well as the clinical

[1] *American Journal of the Medical Sciences*, 1895, cx, p. 631.
[2] *Ibid.*, May, 1905.

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features so closely simulated acute leukæmia that a positive diagnosis of purpura hæmorrhagica could not be made. The leukocytes were 4000 per cmm., and the differential count showed polynuclear leukocytes, 22 per cent.; lymphocytes, 66.5 per cent.; and large mononuclears, 11.5 per cent. The absence of any signs of such an infection, and the fact that the large lymphocytes with "azur-granules," which seem to be characteristic of acute leukæmia, were not found led Hastings to conclude that leukæmia could be excluded. Bezancon and Labbé comment upon the resemblance of purpura hæmorrhagica to acute leukæmia, and group it among the pseudoleukæmias. Cases of aplastic anæmia have usually come to autopsy with the diagnosis of purpura hæmorrhagica.

Scurvy and purpura have frequently been confounded. The chief diagnostic sign of scurvy is not bleeding from the gums, as is commonly taught, but a brawny hemorrhagic infiltration of the thigh or lower leg—the so-called scorbutic scleroderma. Bleeding from the gums is not uncommon in purpura; in fact, it was noted in 23 of this series. Sponginess of the gums, on the other hand, is characteristic of scurvy and very rare in purpura. If the patient is well nourished and has had a varied diet, scurvy need not enter into consideration in making the diagnosis. In some cases the diagnosis can only be made by observing the therapeutic effect of the addition of fruit and fresh vegetables to the diet. In scurvy there will be speedy and marked improvement.

Hæmophilia is an hereditary and congenital disease, and the family and past history rather than the condition at the time of observation should be the basis of a differential diagnosis. Hayem has shown that the blood platelets are not diminished in hæmophilia. Coagulation is delayed, but the clot contracts normally.

Prognosis.—In nephritis and cerebral hemorrhage, not in loss of blood, lies the chief danger of purpura. Nephritis occurs most frequently in Henoch's disease; the hemorrhagic type is the one commonly seen. Recovery is the rule even when the albuminuria exists for six months or longer. The development of chronic interstitial nephritis is rare. In 4 of our 14 fatal cases death was due to cerebral hemorrhage.

Treatment.—Willan, a century ago, realized that simple methods were of more value than drugs in the treatment of purpura. He said that "without air, exercise, and an easy state of mind the effect of medicine is very uncertain."

Rest.—Experience has taught that rest in bed is the first essential. The coöperation of the patient should be secured, so that he may take the rest treatment willingly. In afebrile cases, as well as in those with fever, the patients should not be permitted to sit up until some time after purpuric crops have ceased to appear. The bed should be placed out-of-doors if possible, and it would be well for the patient to spend both night and day in the fresh air. Care should be taken to avoid an unnecessary weight of bedcovers, although naturally the patient should be kept warm. The attendants should be impressed with the importance of handling the patient gently, as sometimes slight pressure on any part of the body is followed by bleeding into the skin. Unusual care should be taken to keep the under sheet perfectly smooth. Every effort should be made to obtain cheerful surroundings for the sick person and to produce "the easy state of mind" which Willan emphasized as so important.

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Food.—The diet must be light and varied during the active stage of the disease. Foods prepared from milk form a large share of the proper diet. Fresh fruit and some fresh vegetables should be allowed. During convalescence a fuller diet is indicated. Foods rich in iron should be taken.[1] Laxative foods, such as preserved fruits, apple-sauce, honey, and orange marmalade should be given for constipation. If necessary to resort to drugs, mild laxatives, such as cascara sagrada, and castor oil can be given, but salines should be avoided.

Hydrotherapy.—While the purpuric rash is present friction of the skin is contra-indicated. During this period daily warm, full baths should be used. The temperature of the water should be accurately determined, beginning with a bath of 95° F. of ten minutes duration. Later the temperature may be lowered a degree a day until 87° or 85° is reached. Sulphur baths are used in some of the Paris hospitals. Litten strongly recommends warm carbon dioxide baths or warm salt baths in conjunction with arsenic.

Fowler's solution gives excellent results in many cases. It should be administered in increasing doses, and it is well to combine its use with carbon dioxide baths (400 or 500 cc. HCl to 800 or 1000 grams of Na_2CO_3), which should be given four to six times a week. The proper preparation and employment of carbon dioxide baths is described in Matthes' *Lehrbuch der Hydrotherapie*. For the arthritic pains little relief is usually obtained from the salicylates. Their effect, however, may be tried. Phenacetin or acetanilid may be of service. Priessnitz compresses should be applied to the painful joints. Sulphuric acid was employed by Werlhof and recommended by Willan, and aromatic sulphuric acid seems to be of use in checking the hemorrhage. Henoch, who at one time thought that ergot was of great value, later came to a different conclusion. Osler advises the use of oil of turpentine.

Calcium lactate should be used in every case of purpura hæmorrhagica. Boggs has shown experimentally its value in increasing the coagulability of the blood. Coe used it with remarkable success in cases which calcium chloride failed to benefit in 15 grain (1 gm.) doses three or four times a day. According to A. E. Wright, the use of the calcium salts should be stopped after three or four days, as continued use may diminish the coagulability of the blood. In some of our severe cases the use of calcium salts was of no benefit.

In bleeding from the mouth or nose, irrigations with 2 per cent. gelatin or 1 to 1000 adrenalin should be tried. When there is hemorrhage from the œsophagus or stomach, a teaspoonful or less of the 1 to 1000 solution may be swallowed. The adrenalin is decomposed in the stomach and hence does not enter the circulation. Swallowing bits of ice may be tried in hæmatemesis. The use of gelatin subcutaneously is painful, and there is some danger of tetanus resulting unless the gelatin is most thoroughly sterilized. Iron is indicated during convalescence. At this time a stimulating wet mitt friction in the morning and a sedative full bath (90° to 95° and ten to twenty minutes duration) at night are useful. In chronic cases a change of climate is advisable.

[1] The amount of iron in milligrams contained in 100 grams of dry substance: spinach. 35 mg; yolk of egg, 22; asparagus, 20; beef, 17; apple, 13; carrots, 9; beans, 8; potato, 6; rice, 2; (Bunge).

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HÆMOPHILIA.

Definition.—Hæmophilia is an hereditary constitutional anomaly characterized by severe, often uncontrollable bleedings. The condition is usually congenital. The hemorrhages usually result from trivial cuts or bruises, or they may appear spontaneously; the association of bleedings with joint swellings is characteristic.

Historical.—Modern research has failed to reveal any indication that hæmophilia was known to the ancient Greek or Latin medical writers. A solitary reference to the hemorrhagic diathesis in classical literature is found in the *Pharsalia* of the poet Lucan. There is a passage in the writings of the Arabian physician Albucasis, or Alsaharavi, who died at Cordova in A.D., 1107, which refers to a disposition in the males of certain families to severe hemorrhages. We can well understand the feeling that led him to characterize this remarkable tendency to hemorrhage as something "monstrous." In the centuries that elapsed from the time of Albucasis until 1784, when Fordyce's article appeared, no advance was made in the knowledge of hæmophilia. This was fortunate, for, as Grandidier has pointed out, if hæmophilia had been recognized in the dark days of the witchcraft delusion, it would have gone hard with the victims of this disease. Fordyce noticed the occurrence of the hemorrhagic tendency in several individuals belonging to the same family.

To American physicians belongs the credit of first accurately describing the disease and of reporting a considerable number of typical cases. The first of the American articles was published by John C. Otto in 1803.[1] In this paper the term "bleeder" was first used in print, although it is evident that the word was not applied first by Otto, as is stated by many authors. It had probably been long used by the members of hæmophilic families. This is clearly indicated by Otto's statement: "Some persons who are curious suppose they can distinguish the bleeders, *for this is the name given to them.*" The name hæmophilia was given by Schönlein.

The first bleeder of whom we have any detailed record was Oliver Appleton, who lived in Ipswich, Mass., in the early part of the eighteenth century. He was the father of the large Appleton-Swain family. An account of this remarkable family is contained in the excellent paper of John Hay, which was published in 1813. He gave the history of fifteen descendants who were bleeders. The family which Otto described lived in the village of Plymouth, in New Hampshire, and was probably a branch of the original Appleton family. A record of the early American literature of this subject will be found in a monograph by Dunn[2] and in Osler's[3] article.

Etiology.—Hæmophilia has been termed by Grandidier "the most hereditary of the hereditary diseases." It is rare in individuals that do not have a family history of bleeding, and a striking feature is the occurrence of large numbers of cases in the same family. Grandidier's statistics show that if the total number of reported cases of hæmophilia is divided by

[1] *New York Medical Repository*, 1803, vi, p. 1.
[2] *American Journal of the Medical Sciences*, 1883, lxxxv, p. 68.
[3] Pepper's *System of Medicine*, Philadelphia, 1885, iii, p. 938.

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the number of families in which they occurred, the average number of bleeders to a family is three. In the Mampel family there have been thirty-seven bleeders during the last four generations (Lossen). The direct transmission of the disease from parent to child is unusual. In the majority of instances it skips a generation. This atavistic tendency was recognized by John Hay, the early New England physician, who thought there were no exceptions to the rule. In 1813 he wrote: "The children of bleeders are never subject to this disposition, but their grandsons by their daughters." This intermittent heredity is usually explained by the remarkable predilection of the disease for males. The tendency to hemorrhage is generally transmitted by females, although these "conductors," as they are called, do not themselves exhibit a trace of the disease. So it happens that the daughter of a hæmophilic family is exempt herself from the diathesis, but after her marriage she gives birth to sons who are bleeders and to daughters who are not bleeders themselves, but are destined to transmit in their turn this heritage to their unfortunate children (Rochard).

Grandidier, in his second edition of his monograph (1877), was able to collect in all 609 male bleeders and 48 female bleeders, a ratio of 13 to 1. Dunn, in 1883, in a study of 780 hæmophiliacs, found 717 among males and only 63 among females, a ratio of 11 to 1. During the past two decades a number of hæmophilic families have been studied in which a much larger percentage of the bleeders were females. Stempel[1] found 209 cases reported between 1890 and 1900, of which 167 were in men and 42 in women, a proportion of about 4 to 1. Within the past seven years additional families have been described in which the ratio of male to female bleeders was still lower—Pearson,[2] Blake,[3] Türk,[4] Goodall,[5] Neumann,[6] Larrabee,[7] Bramwell.[8] In the family studied by Bramwell four of the bleeders were females and only two males. Faludi states that nearly a third of the cases are in females.

The Appleton-Swain family of bleeders was the first to be carefully studied. In John Hay's paper there is an account of 18 bleeders among the descendants of Oliver Appleton. At the time he wrote 7 had died of the disease. The tendency was transmitted through females, but only males exhibited a hemorrhagic disposition. Most of the bleeders of this family lived in Reading, Mass., a small town near Boston. Osler's inquiry, made in 1885, revealed the fact that a young lad, Warren Coburn, a bleeder, had died about twelve years previously. This was an instance of the transmission of the disposition to the seventh generation within a period of two hundred years. Dr. Brown stated at that time that in the vicinity of Reading there were no Appleton or Swain families which contained bleeders. The writer has written to the physicians of Reading, but has been unable to learn of any bleeders living there during the past twenty-five years. The disease disappeared long ago from the village of Plymouth, where lived the first family

[1] *Centralblatt für die Grenzgebiete der Medizin und Chirurgie*, 1900, iii, p. 721.
[2] *Lancet*, 1904, i, p. 91.
[3] *British Medical Journal*, 1904, i, p. 189.
[4] *Centralblatt für innere Medicin*, 1902, xxiii, p. 218.
[5] *Scottish Medical and Surgical Journal*, 1905, xvi, p. 133.
[6] *Prag. medic. Wochenschrift*, 1900, Nr. 38.
[7] *American Journal of the Medical Sciences*, 1906, cxxi, p. 497.
[8] *Clinical Studies*, Edinburgh, 1907, v, p. 398.

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of bleeders whose cases were reported in any detail. The physicians in that town write that no instance of the disease has been seen in recent times.

In Goodall's case the transmission was through the male line, but in the fourth generation the disease showed most markedly in the female members. Förster cites a singular instance in which only females bled and the boys were quite free from the disease. Limbeck, Neumann, and Gocht have observed cases in which a woman was subject to the disease and also transmitted it.

In the remarkable Mampel family of Kirchheim, near Heidelberg, the disease has been carefully studied for nearly a century. The first report was

FIG. 60

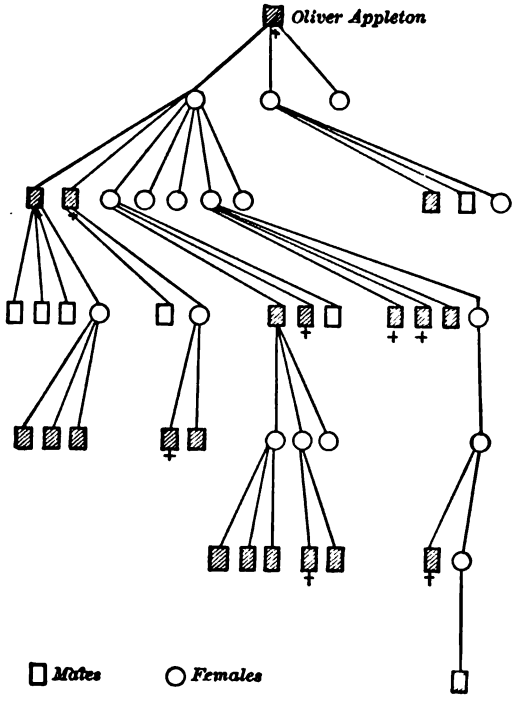

Chart of the Appleton-Swain family of bleeders, showing the transmission of the tendency to the seventh generation within two hundred years. The shaded figures represent bleeders and death from hemorrhage.

published by Chelius in 1827, then by Mutzenbecher in 1841, by Lossen in 1876, and by Lossen again in 1905. Of the 111 male members of that family, 37 have been bleeders (33⅓ per cent.). Excluding those branches of the family that contain no bleeders, the number of affected male individuals rises to nearly one-half. In the first generation it was 50 per cent., in the second 68 per cent., in the third it fell to 41 per cent., and in the fourth to 32 per cent. In the little Alpine hamlet of Tenna the disease has existed through six or seven generations, and Vieli found 15 to 20 hæmophiliacs

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living there at one time. The form of heredity seen in hæmophilia is not peculiar to this disease. In color blindness and also in night blindness transmission is likewise through the females, while the males alone exhibit the abnormality. Gee has observed a similar mode of transmission in diabetes insipidus, and it is said to occur in ichthyosis and in pseudohypertrophic muscular paralysis. The extraordinary fecundity of hæmophilic families has been noted by many writers. The disease is much more common in northern countries than in southern. About twice as many cases have been observed in Germany as in any other country. Comby, an authority on the disease, comments on the rarity of its occurrence in France. Of 209 recent cases collected by Stempel, 96 were German and 95 English or American. In tropical countries it is practically unknown. Schlesinger stated recently that the disease is common in the neighborhood of Vienna. It is rarely seen in the Boston clinics. Among the last 98,000 patients in the Massachusetts General Hospital Out-Patient Department there has been only one case that was probably hæmophilia.

The disease usually manifests itself within the first two years of life, and an onset after twenty-two years of age is rare. Bleeders are for the most part blondes with fine transparent skin and blue eyes. These characteristics are common in the Teutonic race. On the other hand, brunettes have not uncommonly been subject to hæmophilia. Although bleeders are said to be frequently apathetic, they may be vigorous and alert. Otto and Hay state that the American bleeders under their observation were of florid countenance and extremely irascible. There is no evidence that consanguinity plays any role in the development of hæmophilia. Steiner and Hadlock have reported cases of hæmophilia among negroes. Hæmophilic subjects are frequently of a pronounced neurotic temperament. The nature of their malady and the care they must exercise to avoid the slightest trauma would tend to produce self-absorption and favor the development of psychoneuroses.

Pathogenesis.—For many years authors attempted to explain the disposition to hemorrhage as the result of an abnormal fragility of the vessels. A few anatomical observations supported this position. Virchow and others in a few cases found the vessel walls to be remarkably thin, and a fatty change of the vessels was also described. The observation of Virchow, that the aorta and other vessels were not only thin but narrow, was regarded as most important as throwing light on the pathogenesis. The fact that Virchow himself described the same abnormality in chlorosis would indicate that it had little significance in either of these widely different diseases. As Sahli has pointed out, weakness of the vessel walls, even if a constant finding, would not explain the long-continued bleeding. As a matter of fact, in the great majority of instances the gross and microscopic examination has failed to reveal any alteration in the bloodvessels. In isolated cases proliferation of the endothelium and an embryonic condition of the smaller vessels have been described, but these changes, if found in every case, would not explain the clinical features.

According to *Immermann's theory* there was a congenital disproportion between the large volume of the blood and the small capacity of the bloodvessels. This disproportion was supposed to produce an increased blood pressure. As a result of the high blood pressure it was assumed that hemorrhages would readily occur. This theory received some support from the

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thinness of the vessels described by Virchow and the fact that the left ventricle was found hypertrophied by Schönlein, Schneider, and Gavoy. A fatal objection to this explanation has recently been discovered. In a number of cases of typical severe hæmophilia the blood pressure has been found not increased, but actually below normal (Sahli, Scheehan). There is only one case recorded in which it was increased, reported by Gärtner with a blood pressure of 200 mm. Hg. No details are given, so it is impossible to say that other causes of elevation of the blood pressure were absent. *Oertel's theory* was similar to that of Immermann. He regarded hæmophilia as an hydræmic plethora, but brought forward no proof of this.

Sahli's Theory.[1]—This is the only one that is at all in accord with the facts. He believes that hæmophilia is due to a chemical alteration in the walls of the bloodvessels, and is a disturbance of their function and not of their morphology. Morawitz has shown that fibrin ferment is formed by the union of thrombogen and thrombokinase in the presence of calcium. The thrombokinase probably corresponds with the zymoplastic substance of Schmidt. It is present in the tissue juices, and, according to Sahli's theory, it or a similar substance is secreted when the wall of a bloodvessel is cut or otherwise injured. Under physiological conditions the injured vessel wall plays an active part by this secretion in checking hemorrhage. The flow of blood does not cease until the mouths of the cut vessels are closed by thrombi. In hæmophilia the secretion of the vessel wall is entirely inhibited or reduced to a minimum, hence clotting in the mouths of the cut vessels does not occur, as that depends chiefly upon the function of the wall of the bloodvessels in pouring out thrombokinase (Morawitz) or zymoplastic substance (Schmidt). There may be extravascular clotting in hæmophilia, as thrombokinase is formed by the tissue juices as well as by the wall of the bloodvessels. This explains how it is possible for bleeding to continue even when the coagulation time of the blood outside of the body is normal. The deficient coagulability of the blood in the intervals between the hæmophilic bleeding is the result, according to this view, of an altered function in the cells of the blood or of the blood-making organs analogous to that in the cells of the bloodvessels. Sahli furthermore suggests the possibility that it has to do with the general inherited alteration of the cells of the hemophilic organism transmitted through the germ plasm. The chemical change of the vessel walls in hæmophilia explains the origin of hemorrhages if one assumes that this alteration is associated with abnormal fragility or permeability of the vessel walls. The recent studies of Morawitz and Bierich[2] support this theory. They show that the hemorrhagic diathesis that develops in certain cases of jaundice is probably due to changes in the bloodvessels associated with changes in the blood.

Infectious Theory.—W. Koch maintains that scurvy, purpura, and hæmophilia are different manifestations of one and the same disease which is infectious in nature. Too much space is given to this untenable theory in recent treatises on the hemorrhagic diathesis. No one accepts this view; there are few if any facts that support it. Lossen,[3] who has had under observation the large Mampel family of bleeders for a period of over thirty

[1] *Zeitschrift für klinische Medicin*, 1905, lvi, p. 264.
[2] *Arch. für exp. Path. und Pharm.*, 1907, lvi, p. 115.
[3] *Deut. Zeit. für Chir.*, 1905, lxxvi, p. 1.

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years, says that only a man whose knowledge of hæmophilia was acquired entirely from books could arrive at such a conclusion.

Pathology.—An anæmia of high degree resulting from hemorrhage has been the most constant finding at autopsy. Ecchymoses are common. In a few cases the arteries have been small and thin, presenting the appearance of veins. A superficial situation and prominence of the peripheral bloodvessels has been described. Proliferation of the endothelium of the small vessels has been noted in a few instances. Hypertrophy of the left ventricle of the heart is not uncommon and was present in 3 of 4 cases studied recently by Sahli. Fatty degeneration of the intima of the larger arteries and of the heart may occur. These vascular changes are probably without significance. In the majority of cases examined the heart and bloodvessels have been normal. In support of his theory of an infectious origin, W. Koch referred to the splenic tumor which he said was always present in hæmophilia. As a matter of fact, the spleen is rarely enlarged. A persistent thymus has been observed. In Goodall's fatal case Hassall's corpuscles were very large.

The Blood Pressure.—Very few estimations have been made. In one of Sahli's cases it was 115 mm. Hg. (Riva-Rocci). In his other cases it did not seem increased as determined by palpation. In a case reported by Sheehan[1] the blood pressure was only 108 mm. Hg. In only one instance, that of Gärtner, has the blood pressure been high.

Blood.—The number of leukocytes is often diminished (Sahli, Wright). There is both a relative and an absolute diminution in the number of polynuclear leukocytes and a relative increase in the lymphocytes. In Goodall's case the leukocyte count fell to 4400 shortly before death, and the polynuclear leukocytes to 41 per cent. In counting 500 leukocytes, 15 megaloblasts and 40 normoblasts were seen. According to Hayem and Sahli, the number of blood platelets is not diminished. The former states that the retraction of the clot and transudation of serum are normal, which distinguishes the blood in hæmophilia from that in purpura. The mineral constituents of the blood are present in the usual proportion. The fibrin content is not diminished. Heyland found 5, Gavoyritter 2.6, and Otto 4.3 parts per thousand in the hæmophilic blood. These numbers lie within the normal.

Coagulation Time.—Some writers have found the coagulation time diminished, while others have observed cases in which it was normal. F. A. Hoffmann[2] stated that the coagulation was retarded only after much blood had been lost. This is not evidence that the coagulability of the blood is normal in hæmophilia, as he claimed, for Cohnheim showed that under normal circumstances loss of blood increased the coagulability. Sahli made the important discovery that coagulation might be normal or even accelerated in typical cases of hæmophilia while hemorrhage was in progress, and yet distinctly delayed in the intervals between bleedings. This change in the coagulation time at different periods may account for the apparently contradictory statements in the literature.

The coagulation time must be determined with blood from a freshly made wound. Sahli found in one case that blood from a fresh puncture clotted in thirty-one minutes, as determined by Vierordt's method. Blood

[1] *Buffalo Medical Journal*, 1905, lxi, p. 362.
[2] *Lehrbuch der Constitutionskrankheiten*, Stuttgart, 1903, p. 116.

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obtained eleven minutes after the test had begun began to clot in two minutes. He asserts that no one had previously recognized that blood for a coagulation test must be obtained from a perfectly fresh wound. Sahli is not correct in stating that this fact had not been previously recognized. In a paper published two years prior to his monograph the writer said: "A second drop of blood obtained from a cut after the first drop has coagulated always coagulates more rapidly than the first. This occurs also if the skin, after the removal of the first drop, is cleaned carefully with water, alcohol, and ether."[1] Ignorance of this had undoubtedly been a frequent source of error and confusion in estimations of the coagulation time of the blood in disease, especially in hæmophilia. A. E. Wright[2] found the coagulation time retarded in hæmophilia, in one instance forty-five minutes, in another over an hour. In Goodall's fatal case blood obtained from the femoral vein after death failed to coagulate.

The writer pointed out in 1903[3] that deductions could not be drawn from slight changes in the coagulation time. Observations on the same person, on the same diet, at the same temperature, at the same hour on different days, may give results that vary several minutes. Blood from fresh punctures made from the same part of the body within fifteen minutes or half an hour of each other may show considerable difference in the coagulation time. These results have recently been confirmed by M. Solis-Cohen,[4] who worked with Wright's latest method. The value of Wright's conclusions is impaired by the fact that he did not realize what wide variations may occur in the coagulation time uninfluenced by drugs or diet.

Symptoms.—The essential characteristic of hæmophilia is the occurrence of severe hemorrhages usually following slight trauma, but sometimes developing spontaneously. In the vast majority the disease manifests itself in early life, the first hemorrhage occurring in nearly three-fourths of the cases before the end of the second year. At the time Grandidier wrote no case had been observed in which the onset was later than the twenty-second year. v. Limbeck has since recorded a case in a woman who showed the first signs of hæmophilia in her sixtieth year. During the following fifteen years she suffered from severe and uncontrollable epistaxis, which finally caused her death. She was the mother of a pronounced hæmophilic family. Neumann observed a case in which the first hemorrhage occurred in the forty-second year. These two instances stand out as striking exceptions to the general rule that the symptoms of the disease chiefly manifest themselves during the developmental period of life. The disease does not usually show itself in newly born children; Larrabee was able to collect only 37 instances. Some of these were doubtful, as the clinical histories simply stated that the patient bled from birth. Nine additional cases have been found in the literature. In one observed by Eröss the first bleeding apparently occurred in the uterus before the birth of the child. Hemorrhage in the newly born is usually due to bacterial infections, and bears no relation to hæmophilia. Grandidier collected 228 cases of spontaneous hemorrhages from the navel soon after birth, and of these only 14 (6 per cent.) occurred

[1] *Journal of Medical Research*, 1903, x, p. 121; also *Archiv für exp. Path. und Pharm.*, 1903, xliv, p. 299.
[2] *British Medical Journal*, July 14, 1894.
[3] *Journal of Medical Research*, 1903, x, p. 120.
[4] *University of Pennsylvania Medical Bulletin*, 1907, xx, p. 56.

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in hæmophilic families. The ritualistic circumcision has repeatedly led to the early recognition of hæmophilia, and has often been followed by severe and sometimes fatal bleeding. In hæmophilic families, in addition to the typical cases there may be others in which the tendency to hemorrhage is much less marked. In the family studied by v. Limbeck one of the boys bled slightly from time to time until his sixteenth year, but during his later life exhibited no sign of hæmophilia.

Hemorrhages are grouped according to their origin into spontaneous and traumatic, and according to their position into superficial, interstitial, parenchymatous, and hemorrhages into the body cavities (pleura, peritoneum). To the first group belong hemorrhages from the external skin and mucous membranes. Some recent writers have denied the existence of spontaneous hemorrhages. It is certainly true that many of the instances placed in this class are the result of trauma so slight that it escaped notice. Doubtless a very large proportion of hæmophilic bleedings are really traumatic in origin.

The facts that favor the view that hemorrhages may arise spontaneously are, first, the occurrence of marked prodromal symptoms in certain cases. The following have been described: Restlessness, excitability, flushing and a sensation of warmth in the face, vertigo, dizziness, cardiac palpitation, dyspnœa, and visible pulsation of the arteries or veins of the head. Second, the occurrence of hemorrhage from the kidneys, stomach, and intestines as well as into solid viscera protected from external injury. Stempel cites a case of Eröss in which it would seem that the petechiæ in the skin as well as the occurrence of intestinal hemorrhages immediately after birth must have been spontaneous. The autopsy revealed a hemorrhage in the apex of the lower lobe of the left lung and also in the wall of the colon. The child belonged to a hæmophilic family.

Cutaneous hemorrhages are very frequent; ecchymoses and suggillations are common, but the small punctiform spots (petechiæ) are extremely rare. In Stempel's analysis of the literature of the last decade he found the occurrence of petechiæ noted in only two instances. In a case reported by Dunn there were purpuric spots on the ear, cheek, neck, trunk, and legs, and also on the gums, fauces, and epiglottis. Comby mentions a case in which hemorrhages of the skin of the arm closely simulated erythema nodosum. Bleeding may occur from the apparently normal skin, as in a patient observed by Cohen with repeated hemorrhages from the skin of the uninjured finger tips. Severe hemorrhage is apt to follow slight injuries of the skin, such as scratches, cuts, and blows.

Hemorrhage from the mucous membranes is very common, especially from the nose. Among 334 cases epistaxis occurred in 169 (Grandidier). Bleeding from the gums is frequent and often occurs during the first dentition; in fact, the eruption of each tooth may give rise to a severe hemorrhage. From no part of the body are the hemorrhages more severe and uncontrollable than from the gums. Next in order of frequency are hemorrhages from the bowels, the lungs, and stomach. In rare instances bleeding has occurred from the eyelids, tear papilla, external ear, vulva, and scrotum. In females there may be no sign of the disease until menstruation is established. Bleeding from the uterus has frequently been so severe as to endanger life, and in the case studied first by Townsend and later by Vickery menorrhagia continued for four months and caused death. Childbirth in hæmophilic

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women is frequently followed by great loss of blood, as occurred in 69 out of 150 cases collected by DuBovis. In 2 instances in his series the mothers were unable to nurse their children, as this seemed to increase the tendency to hemorrhage. Döderlein reported a case in a woman who gave birth to nine children; one to two hours after the birth of each child severe hemorrhage began, which continued until the woman was almost bloodless.

The *subcutaneous hæmatomas* are sometimes painless, but may give rise to much suffering and be accompanied by fever and gastro-intestinal disturbances. Sometimes they reach a very large size, and may weaken the patient from loss of blood. In fact, death has occurred from hemorrhage into the tissues unassociated with external bleeding. Hamilton[1] observed a large hæmatoma of the head which did not disappear for over four months. A subcutaneous hemorrhage was seen by Fussell[2] in a child which reached from the axilla to the lower costal margin and from the mammillary to the scapular line. It is a characteristic of hæmatomas in this disease, as Stempel has pointed out, that they tend to spread far from their point of origin. In Ross'[3] case the hemorrhage began at the elbow and gradually extended until it involved the entire upper arm. Pressure of the extravasated blood on the nerves may give rise to severe pain or paralysis. The pulse may be obliterated in consequence of arterial compression. Linser[4] reported a case in which paralysis of the hand followed the disappearance of a hæmatoma from its dorsal surface. *Subfascial* and *intermuscular hemorrhages* are rare, and even more unusual are *hemorrhages into large serous sacs*. Psoas-hæmatomas have been studied by Moses, but are of very rare occurrence. Sometimes in subcutaneous or intramuscular hemorrhage resorption does not occur and a cyst may form, as in a case reported by Virchow.

Hæmatomas in bleeders have frequently been mistaken for phlegmons. Sometimes the differential diagnosis is impossible. Gayet[5] reported a case in a twelve-year-old bleeder in which pain and swelling of the left arm suddenly developed. The swelling rapidly increased, the overlying skin was glossy, tense, and extremely tender. The temperature rose to 102° and the diagnosis of an acute phlegmon was made. Later a second swelling appeared which gave a distinct sensation of fluctuation. An incision was made, but instead of pus only sanguinolent fluid and blood clots were found.

A trivial wound or a mere scratch may be followed by a more serious hemorrhage than a clean cut. This has been noted by many observers. Fordyce claims that he checked a hemorrhage by enlarging the wound with a knife, but this procedure cannot be recommended in dealing with lacerations which bleed seriously, for the reason that fatal hemorrhage has repeatedly occurred during surgical operations on bleeders. The attempt to amputate the bleeding part or to tie an artery in cases of uncontrollable hemorrhage has been followed by death. The blood drips from a wound as it would from a blood-soaked sponge. This type of hemorrhage is often described as parenchymatous, and spurting arteries are never seen. It was noted among the Appleton-Swain family that if several cuts had been inflicted at the same time severe hemorrhage occurred from only one. Osler refers to a bleeder

[1] *New York Medical Record*, November 21, 1891.
[2] *British Medical Journal*, October 30, 1897.
[3] *Ibid.*, April 9, 1898.
[4] *Beiträge z. klin. Chir.*, 1896, xvii, p. 105.
[5] *Gazette hebd. de méd. et de Chir.*, 1895, xxxii.

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who always bled from cuts and bruises above the neck, never from those below.

The hemorrhage usually lasts for hours, and it may continue for days or even weeks. In one of Fischer's cases bleeding continued for three months after the extraction of a tooth; in Vickery's[1] patient it persisted for four months. After severe, long-continued hemorrhage the blood may be almost colorless. One observer states that it would scarcely stain linen. Wounds in bleeders often heal very slowly, and the resorption of blood in interstitial hemorrhages may be long delayed. In fractures of bone union may take place in the usual time (Monsarratt).[2] After a scratch or wound an hour or more is apt to elapse before severe hemorrhage begins. Bleeding from granulating wounds and scars is frequent. Sometimes the most trivial injury, such as a pressure of the hand on the skin or the rubbing of clothes on the body, has been followed by hemorrhage.

General Disturbances.—Cardiac murmurs frequently develop and the pulse may rise to 120 or 140 per minute. It is usually small and weak. Patients are frequently restless, excited, and nervous, and complain of weakness and a sense of oppression across the chest. The tongue is dry, and thirst may be severe. Nausea and anorexia are common, and sometimes there is severe vomiting. Headache and attacks of faintness were observed by Hamilton. In a case reported by Fussell the patient was unconscious for twenty-four hours. The amount of urine may be greatly diminished. Œdema of the face and ankles has been noted repeatedly. Dimness of vision has been described. In long-continued hemorrhages the temperature is frequently elevated.

Several authors have called attention to an abnormal reticence on the part of bleeders to admit their constitutional defect. Dent reported the case of a young bleeder who denied the existence of the disease in himself or in any of his relatives, while bleeding to death as a result of having a tooth pulled. Even in the presence of his mother he stoutly asserted that her statements were false and that he did not bleed more than usual.

Litten mentions the case of a bleeder who, within eleven days, lost twenty-four pounds of blood. Not infrequently hemorrhage continues until the patient faints and the blood pressure falls to a low point. This, as well as the increased coagulability of the blood, tends to stop the bleeding. Bleeders have been repeatedly observed who recover from almost lethal hemorrhages with extraordinary rapidity. In Townsend's[3] case the patient suffered from dangerous menorrhagia, but in eighteen days her health seemed fully restored.

Joint Affections.—They occur with such great frequency that some authors, in their definition of the disease, have mentioned the association of joint swelling with the hereditary tendency to uncontrollable hemorrhage. Linser is probably right in his statement that those bleeders who have not had joint complications are the exception. Stempel found 29 instances in which this complication occurred among the cases reported during the last decade. The early writers recognized the association of hæmophilia and joint symptoms, but they regarded the latter as rheumatic manifestations, and even

[1] *Boston Medical and Surgical Journal*, 1897, cxxxvi.
[2] *British Journal of Children's Diseases*, 1904, i.
[3] *Boston Medical and Surgical Journal*, 1890, cxxiii, p. 516.

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Grandidier held this view. It can be asserted with a good deal of confidence that all the different joint affections from the slightest arthralgia to the severest hæmarthrosis are due to hemorrhage from the synovial membrane into the joint cavity (Stempel). The old view that hemorrhages into the joints occur only in later life is no longer tenable. Within recent years instances have been observed during the first two years of life (Jardine, Eve, Pearce), and a number in which the onset was from the second to the fifth year. Until lately no case of hæmarthrosis had been reported in women, but there are now several undoubted instances on record in females (Cohen, Jardine, Hamilton, Jones).

König's[1] classification of the hæmophilic joints into three stages is generally followed: first, hæmarthrosis, the stage of hemorrhage: second, the inflammatory stage which resembles closely hydrops tuberculosus fibrinosus; third, contraction, scar formation, and ankylosis. Hemorrhage into the joint may take place rapidly, and sometimes within five or ten minutes it becomes greatly swollen. The position of slight flexion or extension may be assumed, but if the blood is absorbed rapidly the affection will not pass into the second stage and the function of the joint may not be disturbed. There may be repeated hemorrhages and all be promptly resorbed. Gocht[2] reported a case in which the patient had more than forty-five severe hemorrhages into the right knee-joint. The blood in each instance had been quickly absorbed and the usefulness of the joint had been but slightly impaired. The left knee-joint, which was contracted, had been the site of about forty hemorrhages, the first thirty-nine being well borne, but the last giving rise to the deformity.

If the blood is not resorbed the swelling of the joint remains, and in spite of every treatment the disease enters the second stage. The overlying skin becomes red and hot; the swollen joint is spindle-shaped, and the resemblance to a tuberculous arthritis is very striking. In this stage the fluid in the joint consists of serum admixed with blood. The synovia are swollen and of brownish color, and a large mass of synovial fringes usually floats in the fluid. The cartilage loses its white color and is stained brown; it is softened and its surface eroded. In rare instances bony outgrowths develop, as in cases reported by Bowlby[3] showing a similarity to the condition in arthritis deformans. König never observed similar changes in the bones. Faludi recently observed a case in which at autopsy there was found slight softening of the bone as well as of the cartilage about the hæmophilic joint. It has been demonstrated by the *x*-rays that an atrophy of the bone occurs, but the thickening of the bone that has sometimes been described is only apparent. In the third stage the cartilage becomes more eroded, and bands of connective tissue unite the opposing surfaces of the joint partially or completely. The capsule becomes contracted and the joint cavity may be entirely obliterated.

Probably very few of the joint hemorrhages are really spontaneous in origin, although some have occurred while the patients were at rest in bed. The thin-walled vessels of the hyperplastic synovial fringes might readily be ruptured by a simple movement of the bone, as has been pointed out by

[1] *Volkmann's Sammlung klinischer Vorträge*, 1892, Neue Folge, Nr. 36.
[2] *Verhandl. d. deut. Gesellsch. f. Chir.*, 28 Kongress, 1899.
[3] *Saint Bartholomew's Hospital Reports*, 1890, xxii.

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Linser and Litten. Small as well as large joints may be affected, and hemorrhages have occurred into the small joints of the fingers and toes. The large joints, especially the knee and elbow, are most frequently involved. Among 32 recent cases collected by Piollet[1] the knee was involved in every instance, the elbow 6 times, and the ankle 12 times. Pain in the joint bears no direct relation to the degree of swelling. The pain may be severe, but in some cases even with marked swelling it has been absent. Fever frequently accompanies the joint attacks. A maximum temperature of 101° or 102° is not uncommon. Sometimes the pain disappears before there is any reduction in the swelling. A few cases have been reported in which the blood disappeared with extraordinary rapidity. In one described by Klemperer the swelling which occurred in the morning disappeared in the evening of the same day. Usually the effusion persists for days or weeks. Spontaneous dislocations of the joint may occur, but there is rarely a high degree of crippling. Linser's case exhibited greater deformity than any other reported; both knees were ankylosed in a position of acute flexion, so that the patient was unable to walk.

Neuralgia and neuritis are common in hæmophilic patients. These symptoms may be explained in part by the pressure of the effused blood on the nerves. Occasionally long-continued fever has been observed which could not be explained by any local finding.

Local Hemorrhages of Hæmophilic Origin.—Bleeders may be affected in early life with hemorrhage from the nose or mouth and later suffer from hæmaturia or bleeding from the bowels. Thus Krimmer's patient had epistaxis and hæmoptysis in childhood, but after the age of eighteen years these symptoms gave place to bleeding from the stomach and intestine. Similar cases have been cited by Ullrich, Bicking, and Uhde. In Lafargue's patient there was first epistaxis and later hæmaturia. Grandidier mentions many undoubted cases of hæmophilia in which epistaxis was the only symptom.

Senator,[2] in 1891, was the first to call special attention to hæmaturia as a manifestation of hæmophilia. His patient belonged to a family of bleeders, and hemorrhage occurred from no part of the body except one kidney. The bleeding was so profuse that the organ was extirpated, and then the bleeding ceased. Careful microscopic examination failed to reveal any lesion in the kidney. G. Klemperer[3] later reported severe hæmaturia in two typical cases of hæmophilia, and a fourth case was studied by Grosglik.[4] In these patients there were no other manifestations of hæmophilia at the time the hæmaturia occurred. The researches of Harris, J. Israel, Hofbauer, Rovsing, Albarran, and others have shown that the so-called essential hæmaturia, or *néphralgie hematurique*, is almost always due to organic changes in the kidney.

Some have denied that Senator's case was hæmophilic in nature; others have objected to the term "local hæmophilia," as they claimed the hæmaturia was simply the local symptom of a constitutional disease. If Sahli's theory be correct, there would be no reason, as he points out, why the injury

[1] *Gazette des hôpitaux*, 1902, No. 39, p. 385.
[2] *Berl. klin. Wochenschrift*, 1901, Nr. 1.
[3] *Deut. med. Wochenschrift*, 1897, xxv.
[4] *Volkmann's Sammlung klinischer Vorträge*, 1898, Neue Folge, Nr. 210

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to the hæmostatic function of the bloodvessels might not be limited to one organ such as the kidney. Senator's view is also strengthened by the observation quite recently of cases of hereditary renal hæmophilia[1] (Attlee and Guthrie, Senator).

Multiple Hereditary Telangiectasis with Recurring Hemorrhages.—The clinical aspects of this remarkable and very rare condition were first described by Osler.[2] For a detailed description of this disease his papers and that of A. Kelly[3] should be consulted. Only about 15 cases were found in the literature by these writers. The case reported by Chauffard[4] should be added to their list. There was a distinct family history of the disease in nearly all the cases. Epistaxis is a striking characteristic of this strange affection. Females and males are affected in about equal number. The bleedings are often of great severity, and one of Kelly's patients died as a result. Osler recorded a case in which 1400 cc. of blood were lost within twenty-four hours. The telangiectases occur chiefly on the face, cheeks, ears, lips, and tongue. They may, however, develop on the hands, arms, neck, and other parts of the body. In size they vary from a pinpoint to a split pea, and may be level with the skin or elevated. They frequently resemble fresh extravasations of blood, and have been mistaken for purpuric spots. Uncontrollable hemorrhage may occur from the spots in the mucous membranes and less commonly from spots in the skin. In nearly all the cases there has not been excessive bleeding from small cuts of the skin or from bruises. Legg's patient showed a tendency to bleed from traumatic causes. Chiari observed a case in which epistaxis occurred only at the menstrual period. W. S. Thayer mentioned to the writer having seen two men in whom bleeding occurred once a month from telangiectatic spots in the mouth.

The relation of this condition to hæmophilia is uncertain, some denying that there is any connection between them. Others have without special comment placed cases of multiple hereditary telangiectasis with bleeding under the term hæmophilia, but they are certainly not typical cases of hæmophilia, for bleeding rarely occurs except from the telangiectases. There are cases of hæmophilia, however, in which hemorrhage occurs only from particular regions of the body. Abderhalden[5] has studied a family who bled from trivial bruises of the mucous membranes, but not from the skin. In Agnew's case, mentioned by Osler in his text-book, bleeding occurred from cuts and bruises above the neck, never from those below. In addition there are the cases of so-called local hæmophilia seen in families of bleeders in whom hemorrhages occur chiefly or entirely from single organs, such as the kidney or nose. Sahli's theory permits of a reasonable explanation of these cases. He believes that in the local hæmophilias the vessels of only a certain part of the body are affected.

In multiple telangiectasis with bleeding there is not only the hypothetical functional disturbance of the vessel wall described by Sahli, but demonstrable morphological changes in certain vessels. It is possible that a further

[1] *Lancet*, May 3, 1902; also Senator, *Nierenkrankheiten*, 2 Aufl., 515, *Nachträge* (cited by Litten).

[2] *Johns Hopkins Hospital Bulletin*, November, 1901; *Quarterly Journal of Medicine*, 1907.

[3] *Glasgow Medical Journal*, 1906, lxv.

[4] *Soc. méd. des hôp*, April 10, 1896.

[5] *Ziegler's Beiträge*, 1904, xxxv, p. 213.

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study of this disease may throw light on the pathogenesis of true hæmophilia. Both are hereditary, and in both the hemorrhagic tendency appears usually in early life, and is not a transitory condition, but a constitutional anomaly. According to Sahli's view hæmophilia is a disease of the bloodvessels primarily. In the ordinary or general hæmophilia, the hæmostatic function of all the bloodvessels is affected, and hence severe bleeding occurs from trivial cuts in any part of the body.

The investigations of Coe would seem to show that multiple hereditary telangiectasis is a disease of the blood as well as of the bloodvessels. He found the blood platelets greatly reduced in number, and remarkable improvement occurred in both of his patients from the use of calcium lactate. The assumption that in this type of telangiectasis the only change is a morphological one in the vessels does not explain the frequent recurrence nor the severity and duration of the hemorrhages. The persistence of the bleeding is probably due to some abnormality in the coagulability of the blood in the mouths of the open vessels. It is important to have the blood platelets counted in more cases of telangiectasis and of hæmophilia. If found constantly diminished in the former disease and present in normal number in the latter, it would seem to indicate an essential difference between them.

Diagnosis.—Many conditions are mistaken for hæmophilia, but a genuine case of this disease is rarely confused with anything else. It should always be borne in mind that hæmophilia is an hereditary disease and one that usually manifests itself in early childhood. No single hemorrhage, no matter how severe, will warrant the diagnosis of hæmophilia. It is a persistent hemorrhagic diathesis, and can be sharply distinguished from the other forms, which are of short duration, although it may be very difficult and sometimes impossible to distinguish between hæmophilia and certain cases of chronic purpura. The writer saw two such cases with J. W. Coe in New York which he has reported. The first patient was a youth aged seventeen years. The family history was entirely negative. Since the age of five years he had had frequent profuse attacks of epistaxis recurring at irregular intervals, sometimes lasting for hours and causing him to faint. The gums and mucous membrane of the mouth at times oozed blood. The severe attacks had usually been accompanied by numerous purpuric spots over the face and extremities. He had had frequent attacks of rheumatoid pains in the knees, usually accompanied by fever, and an outbreak of petechiæ on the legs. The slightest bruise was invariably followed by an ecchymosis. After having a tooth pulled he bled profusely for three hours. The second was a man aged thirty-one years in whom there was no family history of hæmophilia. When six years old he bled profusely for hours after having a tooth pulled, and two years later began to suffer from frequent attacks of epistaxis, which continued until he came under observation. Any slight bruise was always followed by a subcutaneous hemorrhage.[1]

The coagulation time in these patients was normal. The number of blood platelets was found to be greatly reduced, even at a time when the patients were free from hemorrhage (one 29,000 per cmm. and the other 22,000 per cmm.; the normal being about 450,000). In distinguishing between chronic purpura and hæmophilia blood examinations may prove of the greatest value. In severe cases of purpura the number of blood plate-

[1] *Journal of the American Medical Association*. October 6, 1906.

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lets is greatly reduced, while according to Hayem and Sahli a normal number is found in hæmophilia. The coagulation time in hæmophilia is usually retarded. Even when the blood clots quickly during a bleeding it may show deficient coagulability in the intervals between hemorrhages (Sahli).

In purpura hæmorrhagica the blood clot loses its power of retraction and there is no transudation of serum, while in hæmophilia the retraction of the clot and transudation of serum take place in the normal manner (Hayem). Hemorrhage in the newly born is rarely a manifestation of hæmophilia. Larrabee[1] accepts a case as such (*a*) if there was a distinct history of this disease in the family, or (*b*) if the baby recovered, but in after life remained a bleeder. Infectious (bacterial) hemorrhagic disease of the newly born might develop in a child born to a family of bleeders. Hence a fatal case should not be accepted as hæmophilia unless the possibility of an infection is ruled out.

Recurring epistaxis frequently occurs in other conditions than hæmophilia, but it is possible, as Grandidier has shown, for epistaxis to be the sole manifestation of hæmophilia for years in members of typical hæmophilic families. In the remarkable case reported by G. Klemperer, already mentioned, the patient, belonging to a family of bleeders, for nineteen years suffered from recurring attacks of hæmaturia without exhibiting any other sign of the disease. At birth there had been severe hemorrhage after tying the cord, in childhood epistaxis was common and he bled in consequence of slight trauma, and during the early years of life he had repeated attacks of acute swelling of the joints. It should be remembered that hæmophilic hæmaturia is of very rare occurrence, and it should not be confused with the transient hæmaturia which results from severe exertion or trauma, or with that due to other diseases.

The so-called purpura rheumatica is sometimes confused with hæmophilia, but the joint affections of the two are entirely different. There is not a single case on record in which the joint affection in hæmophilia has been demonstrated to be other than hæmarthrosis, while there is not a single case of undoubted purpura rheumatica in which hemorrhage into the joint has been proved. The joint swelling of hæmophilia may simulate tuberculosis very closely. The value of tuberculin in such cases was well shown by König[2] in a patient who, in addition to the joint affection, suffered from lupus and tuberculous epididymitis. The lupus and the epididymitis reacted markedly to tuberculin, while the affected joint did not show the slightest reaction. The diagnosis of a hæmophilic joint is confirmed by the appearance of ecchymoses beneath the skin subsequent to the swelling.

Prognosis.—Every hemorrhage in an individual in whom the hæmophilic tendency is pronounced endangers life, but bleeders rarely die from their first hemorrhage (Osler). Childhood is the most dangerous period, and the old view that children rarely died during the first year cannot be held any longer, as in the recent collection of cases by v. Etlinger[3] more deaths occurred during the first year than at any other time. According to Grandidier, among 152 hæmophilic boys, 81 died before the end of the seventh year. With sufficient care middle life would seem to be within

[1] *American Journal of the Medical Sciences*, March, 1906.
[2] *Volkmann's Sammlung klinischer Vorträge*, 1892, Neue Folge, Nr. 36.
[3] *Jahrb. f. Kinderheilkunde*, 1901, liv, p. 24.

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the reach of many bleeders (Legg), and the longer one survives the greater the chance of outliving the tendency. This favorable termination is unfortunately rare, and Legg was able to collect only 9 cases, although there are instances in which bleeders have lived to old age. As the disease presents itself in manifold types varying from the mild to the severe, the prognosis in each individual case is to be based solely on the patient's past experience and that of his family.

Treatment.—The members of a hæmophilic family should be strongly advised not to marry, or marriage should be restricted in the majority of instances to the sons, as it has been shown that the disease is generally transmitted through the females, although recent observations have shown that this tendency may pass along the male line more frequently than was formerly thought. The desire to marry has usually proved stronger than the consideration of the danger of bringing hæmophilic children into the world, and so long as the effort to prevent the transmission of this disease to the next generation rests upon the physician's advice without the aid of legal enactment, it does not seem likely that the number of bleeders will diminish quickly. No surgeon should begin an operation and no dentist should pull a tooth until it has been ascertained that the patient is not a bleeder. In hæmophilic families the children from birth should be protected from every injury, and no surgical operation should be allowed. Running, jumping, and active games should be forbidden. The teeth should receive most careful attention, but no tooth should be pulled. Bleeders should always live the simple life, and aim by ordinary hygienic measures to increase their strength and vitality. For improving the general condition cold douches, massage, and dry frictions should be given. Iron, quinine, arsenic, and syrup of ferric iodide have been used for this, but hydrotherapeutic procedures are preferable, sea-bathing being of special value. The food should be simple and nutritious. It is well to give the patient considerable milk, which Wright and Knapp believe accelerates coagulation.

The disease is extremely rare in warm climates, and residence in the South during the winter should be advised. Comby states the case of a patient who bled profusely in Paris, but when taken to Nice the hemorrhages stopped only to recur again upon returning to Paris. If Wright be correct in his view that citric acid diminished the coagulation of the blood, then one would think that the lemonade and orangeade treatments, which have been popular in bleeding families, would have anything but a favorable action. Inorganic acids, particularly sulphuric acid, have been used for many years by German physicians.

Remarkably good results have been reported by Wright and others with calcium chloride and calcium lactate, but in Legg's experience calcium chloride did not definitely lessen the hemorrhagic tendency. Calcium lactate should be employed rather than calcium chloride, as good results have been reported with the lactate after treatment with the chloride had produced no improvement. The former is tasteless while the latter frequently produces nausea. The usual dose of calcium lactate is 1 gram (15 gr.) thrice daily. Wright states that calcium should be omitted every few days or delay instead of acceleration of the coagulation will result; but in some of the cases reported in which the apparent effect was most striking, the drug was given without intermission. If the hemorrhage is severe a larger dose than 15 gr. is indicated. In one case 50 gr. of calcium lactate

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were given in a single dose by Coe, and bleeding ceased in half an hour. Between the intervals of hemorrhage it would be well to give calcium lactate for a day or two every week. Coe in his cases of chronic purpura which simulated hæmophilia, and in two cases of hereditary telangiectasis with bleeding, found that 30 to 40 gr. once or twice a week were sufficient to prevent a recurrence of the hemorrhages.

Calcium chloride has been used locally, absorbent cotton or gauze soaked with a 1 or 2 per cent. solution being applied to the wound.

Sodium sulphate was held in high esteem by the early American hæmophilic families and their physicians.

Grant reported good results in one case by the use of ovarian extract.

Upon the onset of hemorrhage compression is naturally the first thing to try if the site of bleeding is accessible. Plugging the nostrils or packing the uterus with tampons is frequently necessary. Osler mentions the ingenious device of one of his patients who inserted a finger of a very thin rubber glove into the anterior nares and by means of a small bit of rubber tubing blew out the finger, then turned a stopcock, and in this way successfully plugged the nostril. Many writers advocate the application of ferric chloride to the bleeding surfaces, but Sahli and Legg[1] do not favor its use.

Hemorrhages have been repeatedly checked by the application of gauze compresses soaked with a sterile solution of gelatin. Sahli employed a 2 per cent. gelatin solution, but a 5 per cent. solution is recommended by other writers. Gelatin given by the mouth is of questionable value; it has been given frequently with fruit juices. Hesse gave daily for a period of six months 200 grams of a 10 per cent. gelatin solution with good result. This method of administering gelatin is harmless, but the same cannot be said of the subcutaneous injection. Not only is this procedure painful, but gelatin may contain tetanus spores which are not destroyed except at a very high temperature. Furthermore, severe hemorrhage may be produced in hæmophilia from the puncture wound made in injecting the gelatin. If gelatin is employed subcutaneously or applied locally to the wound, great care should be taken to sterilize it thoroughly. The experiments of Boggs failed to show that gelatin reduced the coagulation time of the blood. It is quite possible, as Sahli has suggested, that the gelatin solution applied to the bleeding surface under pressure, such as is exerted by the bandage, enters the mouths of the open vessels and there favors the union of thrombogen and thrombokinase. In one of Sahli's cases the coagulation time was much accelerated, and yet bleeding continued. It was checked by the application of a gelatin compress.

Schäfer has recommended the addition of calcium chloride and adrenalin to styptic lotions. Among other measures that may be resorted to for checking the hemorrhage are the actual cautery, and 1 to 10 per cent. solutions of cocaine and 1 to 1000 adrenalin. Wright advises the local use of carbon dioxide gas and also of oxygen. Hot foot baths (110° to 115°) may be of service in preventing the recurrence of epistaxis. Manteuffel succeeded in controlling a hemorrhage in one case by the watery solution of Schmidt's zymoplastic substance which probably corresponds to Morawitz's thrombokinase. Whether the hæmostatic substance prepared by Landau from the

[1] Allbutt's *System of Medicine*, 1898, v, p. 548.

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spleen by autolysis and to which he has given the name "stagnin" will prove of value is doubtful.

Weil recommends the injection of human or beef serum in hæmophilia. To prevent hemorrhage in the adult 10 to 20 cc. of fresh serum were injected into the veins, or 20 to 30 cc. under the skin. Touissant has found antitetanic and antidiphtheritic sera of equal value. Broca arrested hemorrhage from the socket of a tooth in a hæmophilic child by plugging the cavity with gauze soaked with antidiphtheritic serum, and injecting 20 cc. of serum under the skin. Perthes checked severe hemorrhage from the gums which had lasted for three weeks, by the injection of defibrinated blood of a rabbit into the tissues about the bleeding point. Bleeding recurred, but was controlled by the application of gauze soaked in defibrinated rabbit's blood. Bienwald withdrew some blood from the median vein of a healthy person and injected it quickly into the bleeding wound of a hæmophilic patient. The foreign blood coagulated and prevented further hemorrhage. He believes that hemorrhage might be stopped by the injection of healthy blood into the tissues about the wound. In one of Klemperer's patients long-continued hemorrhage from the kidney ceased under hydrotherapeutic treatment. He employed neutral full baths beginning with a temperature of 95°, and cold affusions to the kidney region. The temperature of successive baths was gradually lowered until 75° was reached.

Joint Affections.—When fresh hemorrhage into the joint occurs, the patient should be kept absolutely quiet in bed. According to Gocht the periods of rest should be interrupted by intervals during which the patient is allowed to walk about. A few days after the onset of the hæmarthrosis a portion of the limb proximal to the joint may be massaged, but not the joint itself. The pain is diminished and absorption of the blood quickened, and the massage tends to prevent muscle atrophy. Puncture of the joint is only employed if the pain becomes unbearable. Gradual extension should be applied to joints that have reached the third stage—that of contraction. This may be obtained by the use of an adjustable splint or of plaster.

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PART III.

DISEASES OF THE SPLEEN, THYMUS, AND LYMPH GLANDS.

CHAPTER XVII.

DISEASES OF THE SPLEEN.

By IRVING PHILLIPS LYON, M.D.

PHYSIOLOGY AND THEORIES OF THE FUNCTIONS OF THE SPLEEN.

A KNOWLEDGE of its physiology is essential to a proper understanding of the relations of the spleen to disease. We cannot expect to unravel the intricate relations of the spleen to various morbid processes until we have some trustworthy data upon its normal as well as its pathological functions. Our present understanding of these functions is fragmentary and confused. The spleen has long been an enigma to physiologists and our present views are admittedly hypothetical and tentative. There are few theories relating to its functions that are not combated or contradicted by almost equal authority. In view, then, of the confusion on the subject, it seems advisable to summarize briefly the prevalent views and find what is really known and what is taken for granted or based on conjecture.

Nerve Supply.—The spleen is supplied by nerve fibres from the left splanchnic nerve, through which a control of the size of the organ is maintained. Stimulation of the splanchnic nerves causes contraction of the organ, whereas cutting them causes splenic enlargement.

Movements.—The spleen is known to be abundantly supplied in its trabeculæ and walls with unstriated muscle fibers which rhythmically contract and expand at intervals of about one minute (Roy). These slight rhythmic movements are believed to assist in maintaining the circulation of the organ independently of the arterial blood pressure. In addition to these slight rhythmic movements, the spleen gradually enlarges during digestion, reaching its greatest size during the fifth hour and thereafter slowly returning to its former size by the twelfth hour (Dobson). This movement is probably a vasodilatation with a general relaxation of the musculature of the organ. The significance of this movement in relation to digestion is unknown.

Formation of Red Blood Corpuscles and Leukocytes.—Hæmatopoiesis.—The question whether in postuterine life the spleen ever reverts

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to its normal function of blood formation during fœtal life has been much disputed and may be regarded as still unsettled, though the recent work of Meyer and Heineke, confirmed by Morris, greatly strengthens the assumption of such reversion in function. Meyer and Heineke,[1] in the histological examination of the spleen in 13 cases of severe anæmia (pernicious anæmia, 9 cases; anæmia following sepsis, 2; anæmia from cardiac disease, 1; leukanæmia, 1), found evidence in every case of new blood formation, namely, collections of cells having the characteristics of myeloid tissue, consisting of nucleated red blood corpuscles (normoblasts), myelocytes, and "lymphocyte-like" cells, justifying them, they thought, in believing that the spleen had reverted to its fœtal function of hæmatopoiesis. These observations have been confirmed by Morris,[2] in experimental pyrodin anæmia in rabbits, who concluded that "the changes occurring in the liver and spleen in the experimental animals are similar histologically, so far as the hæmatogenetic cells are concerned, to those seen in the normal rabbit's embryo at certain stages in its development, and it may be assumed, therefore, that the spleen and liver have taken up their embryonic function, *i. e.*, hæmatopoiesis."

Whatever the facts may be regarding the formation of red blood corpuscles, it is generally admitted that the spleen shares with the lymph tissue of the body in general in the formation of lymphocytes.

Destruction of Red Corpuscles.—Hæmolysis.—The spleen has been regarded as especially concerned in the destruction of waste red blood corpuscles and leukocytes. This view is based on a number of facts, chiefly as follows: the presence in the spleen of a large percentage of iron in the form of an organic compound; the deposit in the spleen of quantities of blood pigment in various diseases accompanied by anæmia; the presence in the spleen of large amœboid macrophages containing whole or partly disintegrated red corpuscles and leukocytes in conditions marked by great blood destruction; the evidence of vicarious or compensatory hæmolysis in the new-formed hæmolymph glands after splenectomy (Warthin), etc. These several observations have led most pathologists as well as clinicians to the opinion that the spleen is especially engaged in the function of hæmolysis in pathological conditions, but the pure physiologists have not generally adopted this view. Thus, Howell (1907) concludes that the theory of the destruction of the red cells in the spleen cannot be considered at present as satisfactorily demonstrated.

Proteid Metabolism.—Enzymes.—The spleen has been believed to be actively engaged in nitrogenous metabolism and especially in the formation of uric acid. This has been assumed from the presence in the spleen of uric acid in considerable quantity, as well as other nitrogenous derivatives, such as leucin, tyrosin, taurin, xanthin, hypoxanthin, adenin, guanin, etc. Recently the spleen has been found to contain an enzyme, adenase, which converts adenin into hypoxanthin (Jones, Schenck), but the significance of such a ferment, which at first seemed important in throwing light on the splenic function in proteid metabolism, is apparently weakened by the finding by Schittenhelm, Lang, Burian, and others of the wide distribution of this and other closely related enzymes and their products in various organs

[1] *Verhandl. d. deutsch. path. Gesellschaft*, 1905, Band ix, 224; *Deutsch. Arch. f. klin. Med.*, 1907, Band lxxxviii, 435.

[2] *Johns Hopkins Hospital Bulletin*, June–July, 1907, vol. xviii, Nos. 195–196, p. 200.

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of the body, viz., liver, spleen, pancreas, lungs, muscles, etc. Chittenden and Mendel[1] say: "A special influence on purin metabolism was at one time attributed to the spleen. Experiments by the writers have failed to substantiate such a view. In fact, there is no evidence that the spleen exerts any special influence on either carbohydrate or proteid metabolism in general."

According to the work of Schiff, modified by the subsequent work of Herzen, Lepine, Gachet and Pachon, and others, the spleen has been represented as elaborating and furnishing to the blood a true internal secretion characterized by a definite enzyme which possesses a special affinity for the pancreas, the protrypsin of which it activates and converts into trypsin. Just what practical significance attaches to this augmenting action of splenic enzyme upon the pancreatic zymogen, protrypsin, is at present difficult to determine, but that it has been exaggerated is evident from the experiments of Pawlow, Popielsky and others, who have shown that the "freshly collected pancreatic juice from animals previously deprived of their spleens (dogs and cats) contains large quantities of proteolytic ferment in the form of trypsin" capable of digesting "a quantity of fibrin in thirty to forty minutes at thermostat temperature which filled a test tube 15 cm. high and 1.5 cm. in diameter" (Pawlow).

Relation to Infectious Diseases and Intoxications.—The relation of the spleen to infectious diseases and intoxications is not certain. In many such conditions the spleen is enlarged, congested, and may show acute inflammatory changes as well as sclerosis. Bacteria and protozoa and their toxins not alone produce such changes, as ricin, abrin, various coal-tar products, etc., may effect similar changes. We must admit that we know little or nothing that is certain of the physiology of the spleen in such states, although it seems probable that it in common with the lymphatic structure generally shares in a defensive mechanism against microörganisms and their products in the various infectious diseases, possibly in a special degree on account of the large amount of lymph tissue and its anatomical position in relation to the portal system. Splenectomized animals and human beings have not been found to show a permanent loss of resistance toward infectious diseases.

Action as a Reservoir for the Portal Blood.—The spleen is believed to act as a kind of safety valve or reservoir for the blood of the portal circulation, with which it is in intimate anatomical relation. This function is suggested by its increase in size after digestion and its enlargement in diseases of the heart, liver, stomach, and intestines, attended with portal stasis. It must be admitted, however, that such a mechanical function must be a very subordinate and insignificant one, shared in common, as it is, by the whole portal system.

Results of Splenectomy.—The results following splenectomy in experimental animals as well as in man for various morbid conditions might be expected to throw light on the splenic function and a brief review of such changes seems indicated.

In the first place, all the facts prove that *the spleen is not an essential organ and can be extirpated without permanent detriment.* In man the spleen has been removed for acute conditions such as traumatic rupture and for various chronic morbid processes. In general it may be said that the changes fol-

[1] Osler's *Modern Medicine*, vol. i, p. 711.

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lowing the removal of the spleen for chronic disease are much less marked than those following removal of essentially healthy spleens for acute conditions, as, for instance, traumatic rupture. The difference seems to depend largely upon the establishment of compensatory changes for the lost splenic function. In the case of splenectomy in essentially healthy spleens the compensatory adjustment is pronounced, whereas in long-standing disease of the spleen such compensatory changes may be assumed to have previously developed so that further changes after splenectomy are less evident. The changes referred to are temporary enlargement of the lymph glands, development of new hæmolymph glands, and changes in the blood, principally secondary anæmia and pronounced leukocytosis. The glandular enlargement following splenectomy in man is exceptional, occurring in recognizable degree in only 3 out of 117 cases reported by Vulpius[1] in 1894; the blood changes are much more usual although not constant. The anæmia is generally moderate, unless much loss of blood has occurred at the operation, but the leukocytosis is usually pronounced (15,000 to 75,000), consisting at first of a polynuclear increase and later of a relative lymphocytosis. These changes seldom last beyond a few weeks except the leukocytosis or lymphocytosis, which may be more persistent, and a moderate eosinophilia which is quite common. Other minor changes may also occur, but are unworthy of special note.

The results of experimental splenectomy on healthy animals have been, on the whole, greatly at variance and confusing. Perhaps the most fruitful and suggestive work in this line is that of Warthin[2] on sheep and goats, whose conclusions were as follows:

"1. After total splenectomy in the sheep there is no evidence of regeneration of the primitive spleen or of the new formation of splenic tissue.

"2. The structural changes following splenectomy are: hyperplasia of existing lymphoid tissues, transformation of hæmolymph nodes into ordinary lymphatic glands, and a new formation of hæmolymph nodes out of lobules of fat tissue, and a later proliferation of the red marrow.

"3. There is no evidence of the formation of red blood cells in the lymph nodes after splenectomy.

"4. The function of hæmolysis is taken up first by the hæmolymph node, later by the ordinary lymphatic glands.

"5. The hæmolytic function of the hæmolymph nodes and hyperplastic lymph glands exceeds that of the primitive spleen, causing an excessive destruction of red cells. The resulting anæmia is later compensated for by an increased activity on the part of the bone-marrow. It would appear, therefore, that the removal of the spleen leads to an increased production or retention of some hæmolytic agent usually disposed of by the spleen. The effect of this agent is either to stimulate the phagocytes in the hæmolymph nodes to increased activity, or to change the red cells so that they are more easily destroyed by these phagocytes.

"6. The presence of great numbers of eosinophiles in the glands showing great destruction of red cells seems to point to some relationship between these cells and hæmolysis."

[1] *Beiträge z. klin. Chir.*, 1894, Band xi.

[2] Contributions to Medical Research, dedicated to Victor Clarence Vaughan, June, 1903.

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Warthin's observations on splenectomized sheep and goats have been confirmed by similar findings on dogs by Morandi and Sisto and have been controverted, on the other hand, by Vincent in work on dogs, again showing the inconstant and varying results that have characterized the experimental study of the question from the first. We may conclude, then, in regard to the functions of the spleen, as Pawlow did regarding the bile, that "when a number of insignificant functions are assigned to any organ, it means that we do not know its real function or have not properly appreciated it."

MALFORMATIONS OF THE SPLEEN.

These are not infrequent and may be congenital or acquired as the result of disease or traumatism. Congenital malformations are chiefly of pathological interest, but their recognition may prove of practical value in the avoidance of diagnostic errors. They include the following types:

1. **Absence of the Spleen.**—Few cases are recorded, almost always combined with other anomalies of development.

2. **Small Spleens.**—Spleens, otherwise normal, weighing less than an ounce, have been observed.

3. **Large Spleens.**—Abnormally large spleens have been reported in infants at birth, generally in monsters. Very large spleens in infants and young children are usually, however, instances of secondary enlargement due to syphilis, rickets, etc.

4. **Abnormalities of Shape.—Lobulated, Multiple, and Accessory Spleens.**—The spleen may vary greatly in form. The most common variation is found in the contour of the lower anterior edge, where the usual notch may be multiplied and exaggerated into deep indentations separating tongue-like or rounded processes projecting forward and downward. Such developmental anomalies must always be considered before assigning a pathological significance to extensions and irregularities of the free edge of the spleen. Various furrows may penetrate the spleen in different directions, so marked, in certain instances, as to divide the organ into a lobulated structure, the so-called lobulated spleen. Multiple or supernumerary spleens are not rare. The accessory organs may be single or multiple up to a large number. They are usually small bodies the size of a pea or bean, sometimes larger, and generally are either attached to the main spleen or lie close to it. Exceptionally, they are widely scattered in the abdominal cavity. Thus, in a remarkable case described by Albrecht, of Vienna, an enormous number of supernumerary spleens was found; in the usual situation there was a spleen the size of a walnut with the splenic artery and vein in their normal position; the other spleens were scattered not only in the mesogastrium but also on the peritoneum, as, for example, on the hepatic ligament and on the convexity of the liver; the largest number was found on the mesentery and transverse mesocolon; there were more than thirty in Douglas' pouch: each of these spleens was enclosed in a separate capsule covered by peritoneum and exhibited the gross and microscopic structure of true splenic tissue. As suggested by Warthin, Albrecht's case may perhaps represent not a simple congenital condition, but rather a compensatory process of accessory spleen development, secondary to a congenitally deficient primary spleen or to acquired disease of the spleen.

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5. **Malpositions of the Spleen.**—In association with other congenital defects the spleen may be placed in any part of the abdominal cavity or even, in case of diaphragmatic hernia, in the pleural cavity. In complete *situs transversus* the spleen and liver may be transposed.

Acquired changes in the size, shape, and position of the spleen will be discussed subsequently under the subject of the morbid processes to which they are related.

MOVABLE SPLEEN.

Synonyms.—Floating spleen, wandering spleen, dislocated spleen, splenoptosis, splenectopia.

The normal mobility of the spleen is slight, depending upon movements of the diaphragm to which the spleen is attached by its suspensory ligament. When this becomes permanently relaxed and elongated, the spleen becomes abnormally movable and dislocated downward, constituting the so-called wandering or floating spleen, which, according to the degree of elongation of the pedicle, may occupy any position in the abdominal cavity; it commonly occupies some part of the left side, but it has been found in the bony pelvis, on the right side, and even in the sac of an inguinal hernia.

Etiology.—The causes are those leading to relaxatian of the splenic fixation, as dragging of a large, heavy spleen, pressure and traction exerted by neighboring organs, as an enlarged kidney, dilated and prolapsed stomach or colon, general enteroptosis, weakening of the normal support of the abdominal walls from repeated pregnancies or ascites, trauma, etc. The causes, in general, are similar to those producing movable kidney and general enteroptosis and, as in these conditions, are operative chiefly in the female sex; in fact, movable spleen is frequently only part of a general enteroptosis. Splenic enlargement, alone, must be considered as merely an exciting cause, as otherwise it would lead usually to dislocation, which is contrary to common observation; so also relaxation of the abdominal walls is only rarely associated with dislocated spleen, when the frequency of the former condition is considered. Another factor must, therefore, be assumed, namely, an inherent weakness or predisposition to relaxation of the splenic ligaments, possibly a congenital defect, at least so in many cases, as also in enteroptosis and movable kidney; thus may be explained the occurrence of wandering spleen in several members of a family, sometimes observed. Trauma may only in rare instances be considered a sufficient cause.

Pathology.—The pathological anatomy of the condition embraces both the primary morbid processes acting as etiological factors, which need not be discussed in this place, and the numerous changes depending upon circulatory disturbances in the displaced organ. The spleen may be of normal size in exceptional cases, although it is usually enlarged. The enlargement is not necessarily primary, as secondary enlargement may well be explained by disturbances of circulation leading to chronic congestion and hyperplasia of connective tissue. Rotation of the organ and torsion of the pedicle may occur and several twists of the pedicle are sometimes observed. Progressive splenic enlargement or sudden increase in size may follow strangulation of the pedicle, and even acute necrosis may result, as in a case cited by Osler; on the other hand, chronic sclerosis, partial or general, with atrophy, may

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follow. Perisplenitis may develop and result in fixing the displaced organ by adhesions in its abnormal position.

Symptoms.—These vary greatly. There may be no symptoms whatever and the condition may be discovered accidentally in a routine physical examination; the symptoms are ordinarily surprisingly slight. There may be a dragging sensation or varying degrees of discomfort or pain in the back and side, referred in any direction. The patient often complains of general neurasthenic symptoms, such as headache, insomnia, digestive disturbances, constipation, weakness, nervousness, apprehension, etc. Circulatory and other disturbances in different organs may arise from pressure, traction or adhesion of the displaced spleen; thus, there may be nausea, vomiting, diarrhœa, constipation, jaundice, ascites, bladder and uterine disturbance, etc., depending on the organ interfered with. Intestinal obstruction and strangulation are possible. Twisting of the pedicle may lead to sudden and alarming symptoms, due to strangulation, acute enlargement of the spleen, rapidly developing anæmia, severe pain, fever, persistent vomiting, hemorrhage from the spleen or from the stomach and bowels, with shock and collapse. In case the torsion is more gradually produced or partial, without strangulation, the symptoms are less violent. Acute perisplenitis gives rise to local pain and sometimes to palpable or auscultatory friction.

Diagnosis.—This in most cases is easy. A mass, resembling the spleen in shape, with a sharp indented edge and pulsating artery at the hilus, capable of replacement into the normal position of the spleen, cannot be mistaken. The absence of dulness in the normal location can usually be made out. The position of the displaced organ is apt to be superficial. More difficulty will be experienced if the organ is adherent in its new position or deformed. It has been mistaken for floating kidney, ovarian and uterine tumor, extra-uterine pregnancy, fæcal accumulation, etc. Care in the examination should suffice in most cases to avoid such errors.

Treatment.—This is guided by the morbid process in the spleen, whether primary or secondary, and by the severity of the symptoms. If discovered accidentally and without symptoms the spleen is better left alone. Caution must be enjoined, also, against informing nervous women of its discovery, as symptoms may date from their knowledge of the condition and progressive neurasthenia may be the penalty. In the majority of cases neurasthenic symptoms are complained of and require general psychic, hygienic, and nutritive treatment. These measures may alone suffice and should always be given a thorough trial. In addition to the general treatment, a well-fitted general abdominal bandage or one made with a special pad for supporting the spleen is usually of great benefit and relieves the local distress and pain. Quinine for enlargement due to malaria, and mercury and iodide for syphilitic enlargement should be given a thorough trial in these affections before resorting to more radical measures.

Only in severe cases are *operative measures* advisable, after simpler methods have failed or where dangerous complications and alarming symptoms arise. Stitching the spleen in its normal position, *splenopexy*, and modifications of this operation have been tried in a few cases in recent years. Rydygier formed a pocket out of the parietal peritoneum that covers the normal splenic region and placed and stitched the spleen therein, reporting the organ in position after an interval of three months. Halsted, in two

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of Osler's cases of enlarged wandering spleen, packed the organ in position with gauze, producing firm attachment, so that the spleen was found in position in both cases more than eighteen months after operation. It is still too early for final judgment as to the permanency of the results of splenopexy, but judging from the failure of the analogous operation for floating kidney much permanent good should not be expected from it.

The operation of choice is extirpation, known as *splenectomy*. This has been practised in recent years with increasing success, due to the greater care and better judgment of surgeons in the selection of suitable cases. The operation in such cases, according to Stierin, has a mortality of about 6 per cent. Bessel-Hagen collected 43 cases operated upon in the last decade with only 3 deaths. The usual causes of death after operation are secondary hemorrhage and infection. Leukæmic and amyloid disease of the spleen are contra-indications to operation, as the mortality is excessive. In case the displaced spleen is firmly fixed by adhesions to important structures, non-interference may be deemed the conservative course. Acute strangulation demands prompt surgical relief.

CONGESTION AND INFLAMMATION OF THE SPLEEN.

Synonyms.—Acute and chronic splenic tumor, indurative splenitis.

Definition.—Active or passive hyperæmia, with or without inflammation, acute or chronic in its course, according to the cause and duration. No hard-and-fast line of division can be drawn between congestion and indurative inflammation of the spleen, as both arise from the same causes and occur together as elements or stages of the same processes. This statement applies more particularly in a clinical sense, but even pathologically the two elements are so closely related and interdependent that the distinction of one from the other is difficult or impossible in many cases. Hence it seems advisable clinically to consider them together instead of separately, in order to avoid repetition and involvement in fine-spun distinctions. Of all morbid processes involving the spleen, congestive or inflammatory swelling is by far the most frequent and important observed clinically.

Etiology.—The causes are those of congestion and inflammation in other organs, namely, irritation or local or general stasis. But such causes act in a special degree upon the spleen above all other organs of the body. The reason for this is not clear in the present state of our knowledge. The sluggish circulation of the organ and its conjectural functional relations in certain processes may be supposed to render the spleen especially liable to congestion and irritation. Irritants may produce both active and passive hyperæmia; stasis produces passive congestion.

The most frequent cause of irritative congestion and inflammation is the action of microörganisms and their toxins in the various infectious diseases, *e. g.*, typhoid fever, malaria, syphilis, etc. Less common causes of irritation are the toxic action of drugs, *e. g.*, acetanilide and other coal-tar derivatives, etc., trauma, and local morbid processes in the spleen, *e. g.*, hemorrhage, embolism, etc. Chronic splenic tumor may also arise in various anæmic conditions, *e. g.*, pernicious anæmia, chlorosis, infantile anæmias, etc., and in various diseases of unknown etiology, *e. g.*, splenic anæmia, chronic cyanotic polycythæmia, rickets, etc. The causes of the indurative inflamma-

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tion of the spleen in such states, while unknown, may be assumed to be some kind of irritation produced by excessive blood destruction or by chronic toxæmia.

Stasis, as a cause of splenic tumor, acts mechanically by damming back the outflow of venous blood, and arises from diseases of the heart and lungs, leading to obstruction of the general circulation, or from diseases of the portal area causing obstruction to the portal circulation (cirrhosis of the liver, pylephlebitis, pressure on the portal or splenic veins by tumors, adhesions, etc.).

The causes may act acutely, as in typhoid fever, or chronically, as in splenic anæmia, cirrhosis of the liver, etc., leading respectively to acute or chronic splenic tumor. An acute cause may rarely set up an inflammatory process that continues and becomes chronic, but this is exceptional.

Pathology.—The most evident alteration is in the size of the organ which is enlarged, varying with the cause and the duration of the process. Moderate enlargement is the rule in acute diseases, more marked enlargement in chronic diseases. The enlargement may become excessive, especially in chronic malaria and splenic anæmia. The organ is usually soft and flabby in acute processes, firm and hard in chronic diseases. Besides congestion with hemorrhages, the organ in acute processes shows slight hyperplasia involving especially the Malpighian bodies, which are in consequence prominent, and in some instances areas of hyaline degeneration and focal necroses. Infarcts occasionally develop from thrombosis of the smaller vessels. Perisplenitis is common. Acute suppurative splenitis or abscess is rare. In the more chronic conditions the tendency is to general induration, involving especially the trabeculæ and their vessels. The whole spleen may be converted into a mass of fibrous tissue with little true parenchyma left. The capsule usually shares in the general fibrosis and may be greatly thickened or involved in circumscribed areas of capsulitis with adhesions. Considerable pigmentation of the organ is commonly seen in anæmic states with marked blood destruction and may lead to cyanotic induration. Rupture of the enlarged spleen occurs rarely in malaria, typhoid fever, and other conditions.

Symptoms and Diagnosis.—The only important clinical symptoms are splenic tumor and pain, upon which the diagnosis must be based. Other secondary symptoms may depend upon the primary disease, upon complications arising from the enlarged organ, *e. g.*, dislocation, torsion of the pedicle, perisplenitis, infarct, thrombosis, abscess, rupture, etc., or upon pressure effects on surrounding organs, *e. g.*, digestive, cardiac, and respiratory disturbances, gastric hemorrhage, ascites, etc. Pain over the spleen or sometimes referred in different directions is not a constant feature. It is caused especially by perisplenitis and rapid enlargement with stretching of the capsule. A feeling of weight or uneasiness in the region of the spleen is usually a complaint. Distinct tenderness of the organ is elicited by pressure. Splenic tumor is the only constant sign. It may be difficult to detect if the enlargement is not marked, and the consistence of the organ is soft as in acute splenic tumor. Palpation is in general far more reliable than percussion. In chronic cases the tumor is firm and resistant upon palpation and may reach enormous dimensions.

As splenic enlargement is found in such a variety of morbid conditions, many of them of obscure etiology and complicated symptomatology, the

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recognition of splenic tumor may be of decided diagnostic significance and should never be overlooked or neglected as part of every thorough physical examination. It seems unnecessary to enumerate the morbid conditions and describe the condition of the spleen in each of which splenic tumor may occur as a feature, as such an enumeration would require almost a complete list of the infectious diseases, the anæmias, all conditions attended by stasis of the general and portal circulation, and many affections of unknown nature.

Pulsating tumor of the spleen has been reported as a curious and rare phenomenon in a few cases of acute splenic tumor (Tulpius, Gerhardt, Prior, Drasche). The pulsation could be distinctly felt on palpation and in some instances seen by inspection. The cases, seven in all, presented a combination believed to be essential to the production of the pulsation, namely, acute splenic tumor, secondary to typhoid fever, malaria, rheumatic fever, acute pericarditis, etc., *plus* cardiac disease accompanied by high systolic blood pressure, almost invariably aortic insufficiency.

Treatment.—The treatment is practically that of the primary disease to which the splenic enlargement is secondary. It would be manifestly ridiculous to attempt to treat the "ague-cake" of malaria without curing the malaria with quinine or the splenic hypertrophy of syphilis without mercury and iodide. It would be dangerous to try to reduce the acute splenic tumor of typhoid fever by active depletion of the portal system without regard to the typhoid fever. The cause of the splenic tumor must first be determined and appropriate treatment directed thereto. There are, however, certain special therapeutic indications for the enlargement itself and for its effects.

Free catharsis may in suitable cases tend to reduce the congested spleen and relieve symptoms of acute stretching of the capsule. The pain, if severe, can be relieved by various local measures, including the application of heat or cold, blisters, dry cupping, strapping the side with adhesive plaster to reduce the respiratory movement of the spleen, or by the administration of morphine, if simpler remedies fail. The application of the *x*-rays over the spleen in cases of marked hypertrophy has been followed in many instances by reduction in its size. The range and indications of the use of the *x*-rays are, however, not yet clear. In chronic splenic tumor, even if not of malarial origin, quinine, used in large doses and continued for a long period, has been claimed to be of value by some writers. The iodides may have some slight effect in the non-syphilitic cases. Iron and arsenic are indicated for the chronic anæmia frequently accompanying splenic enlargement and may incidentally have a favorable effect upon the spleen. In cases of doubtful etiology a course of mercury and iodide should be tried and carried to the limits of toleration before abandonment in order to exclude latent syphilis as a cause.

Splenectomy may be indicated in conditions of great splenic enlargement of long standing when all other treatment has failed, in case of severe and repeated gastric hemorrhages, a state of chronic invalidism, various functional disturbances, or special complications. The enlarged spleen of leukæmia and of amyloid disease must be excluded from the indications for splenectomy, as experience has shown that the operation is almost always fatal in these conditions.

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PERISPLENITIS.

Synonyms.—Capsulitis; capsular splenitis; perisplenic peritonitis.

Perisplenitis occurs as an acute, subacute, or chronic process involving the capsule and peritoneal covering of the spleen locally or generally, according to the origin and extent of the inflammation.

Etiology.—The process originates from local disease (infarct, hemorrhage, abscess, gumma, cysts, tumors, etc.) or general involvement (acute or chronic splenitis of the infectious diseases, splenic enlargement from any cause) of the parenchyma of the spleen or by extension from disease outside of the spleen (pleurisy, pneumonia, local or general peritonitis, tumors, cysts, etc.). In old age the capsule may be sclerosed and thickened as part of the process of senile degeneration. Trauma is a rare cause.

Pathology.—The perisplenitis is usually circumscribed, depending upon a focal origin within the parenchyma of the spleen reaching the surface. The lesion may be single or more commonly multiple, several separate points of involvement occurring in the course of the splenic disease to which it is secondary. Where the cause is general or acts extensively, the entire capsule is involved. The peritoneal surface of the organ loses its lustre and is covered with a fibrinous or purulent exudate, according to the severity of the inflammatory process. Adhesions to surrounding structures usually develop from the areas of inflammation and in rare cases may include pockets of pus. Great thickening of the capsule may result at the point of adhesions and cause marked irregularity of the surface of the spleen. Irregularities may also result from contraction of the fibrous areas. The thickening in certain cases may be marked and show a gristly toughness or become calcified in old age. At autopsy the spleen frequently shows circumscribed areas of thickening on its surface, appearing as white opacities, which have been compared with the "milk spots" on the pericardium and, like them, are believed to be caused by attrition.

Symptoms.—The most important symptom is pain limited to the region of the spleen or more rarely referred in different directions. It may be severe, but generally it is less pronounced and may cause only a sense of discomfort. It is intensified by breathing, movements of the body, lying on the left side, or by pressure. It is remarkable, however, how frequently pain is entirely absent in attacks of perisplenitis, as revealed by autopsy. Next to pain, auscultatory or palpable friction is the most frequent sign, and the most reliable. The friction is felt or heard over the spleen during the respiratory movements of the organ or by moving it by pressure exerted by the hand. It has the characteristics of friction occurring in serous membranes elsewhere. It may be difficult to distinguish between pleural friction at the left base and friction from perisplenitis. In rare cases perisplenitis may lead to palpable irregularities of the surface of the spleen. Fever is an inconstant and variable symptom, depending on the degree of the inflammatory process and the morbid condition to which it is secondary.

Diagnosis.—The diagnosis must be based on the presence of pain, tenderness, and friction over the spleen. Irregularities of the surface of the spleen may rarely serve as a guide. Careful differentiation from left-sided diaphragmatic or basal pleurisy must be made, based upon the more definite relation of the pain in pleurisy to the respiration and the associated

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etiological conditions. With firm adhesions the spleen is fixed and does not exhibit its usual respiratory motility.

Treatment.—The pain is relieved by various local applications, such as hot poultices, mustard plasters, dry cupping, or, if preferred, the ice-bag. Strapping the side firmly with adhesive plaster is of service by reducing the movement of the spleen in respiration. If these measures for the relief of pain fail, morphine is indicated. The bowels should be kept active by giving an initial dose of calomel, followed subsequently by salts, as occasion demands. In case of perisplenic collections of pus, surgical interference becomes necessary.

ABSCESS OF THE SPLEEN.

Synonym.—Acute suppurative splenitis.

Etiology.—Abscess of the spleen may occur rarely as an apparently primary condition without discoverable cause. As predisposing causes, exposure to cold, exhaustion, simple trauma, etc., have been mentioned, acting, it is supposed, by lowering the vitality and resistance of the tissue to the growth of accidental organisms circulating in the blood. Infection of the spleen with abscess formation may arise by extension from inflammatory processes in adjacent organs, as from thoracic empyema, perforating gastric ulcer, general or local peritonitis, etc. Putting aside such exceptional causes, the common causes of splenic abscess are septic embolic infarcts and metastatic infection from the circulation in the course of pyogenic infections. Septic embolism arises most frequently from ulcerative endocarditis, in rare cases from abscess of the lung. Metastatic infection of the spleen may be secondary to any inflammatory process in the body from which pyogenic organisms find entrance into the general circulation, *i. e.*, pyæmia. Paget found 39 instances of abscess of the spleen in 430 cases of general pyæmia. Hydatid cyst of the spleen may become secondarily infected and reduced to an abscess cavity. The specific infectious diseases, especially malarial fever, typhoid fever, and relapsing fever, may occasionally cause abscess of the spleen, probably in most instances by secondary infection with the common pus organisms. There is reason, however, for believing that the specific organism of typhoid fever may lead to suppuration of the spleen in isolated instances.

Pathology.—Abscess of the spleen varies commonly from a microscopic collection of pus to one the size of a hen's egg, but in rare instances the entire spleen may be converted into an abscess cavity, containing in one reported case as much as fifteen litres of pus. In such extreme cases the abscess may protrude into and occupy a large part of the abdominal cavity, simulating cyst, ascites, etc. In the non-embolic form the abscess is usually single, large, and likely to be deeply situated in the organ. Embolic or metastatic abscesses are usually small and multiple, sometimes coalescing to form large necrotic areas. They are more likely to be located near the surface of the organ. If the abscess involves the capsule, circumscribed perisplenitis develops, usually with the formation of adhesions to opposing structures which tend to wall off and limit the inflammatory mass and protect against rupture. The localized peritonitis over the spleen may extend and involve the general peritoneum. Rupture of a neglected abscess may take

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place into any adjacent structure, as the general abdominal cavity, stomach, intestine, pleural cavity, lung, kidney, or externally through the abdominal wall, in rare instances leading to recovery by natural drainage. As a rare result, small abscesses have been found encapsulated with their contents inspissated and infiltrated with lime salts, representing a process of natural healing. Suppuration in other organs may develop as part of a general pyæmic state.

Symptoms and Diagnosis.—Abscess of the spleen is a rare condition clinically, being usually discovered at autopsy. In many cases there are no special symptoms to indicate that the spleen is involved. In general the symptoms are those of suppuration elsewhere, with the addition of pain, and tenderness over the spleen and swelling of the organ. When caused by septic embolism the onset is sudden, with all the features of embolism, followed later by the characteristic symptoms of suppuration, namely, pain chills, sweats, irregular pyrexia, leukocytosis with iodophilia, rapidly developing anæmia, emaciation, weakness, digestive disturbances, etc. Such symptoms arising from suppuration in the spleen may be masked by similar symptoms caused by the disease to which the splenic abscess is secondary, *e. g.*, ulcerative endocarditis, pyæmia, etc. In the non-embolic form the onset may be more gradual, but otherwise there may be no difference so far as the spleen is concerned. The spleen is always swollen, its size depending upon the extent of the inflammatory process. In rare cases of large solitary abscess or where the whole spleen is converted into a pus sac, fluctuation of the protruding mass can be elicited. If the abscess exerts pressure against the diaphragm, cough and dyspnœa may be a feature and Litten's diaphragm phenomenon may be present. Perisplenitis is indicated by a friction rub over the spleen. Extension to the general peritoneal cavity is indicated by the symptoms of general peritonitis. Perforation and rupture into other organs are characterized by special symptoms, such as sudden pain and the coughing up of offensive blood-stained pus with rupture into a bronchus, vomiting or passing of pus and blood per rectum with perforation into the stomach or intestine, etc., followed at once by a marked diminution in the size of the spleen. Exploratory puncture has been employed for diagnosis, but its indiscriminate use in diseases of the spleen has led to many fatalities and it should be employed only in carefully selected cases. Examination by the *x*-rays may be of value.

Prognosis.—The prognosis is serious both as regards the abscess itself and the primary condition from which it arose. The embolic abscess is only part of a general pyæmia, which is almost always fatal. Ulcerative endocarditis, the most frequent cause of embolic abscess of the spleen, is also only a variety of pyæmia and is almost necessarily fatal. The non-embolic type may be treated surgically with some hope of success. Spontaneous rupture and evacuation of the abscess through the stomach, intestine, or externally, as described above, may in rare instances be followed by complete recovery. Rupture or extension of the inflammatory process into the general peritoneal cavity, kidney, pancreas, pleural cavity, lung, etc., leads to a variety of complications with rapidly fatal issue. Inspissation of the contents with healing of small abscesses is possible, but is so excessively rare that it hardly influences the prognosis.

Treatment.—The only treatment of any importance is surgical—aspiration of the contents by puncture, incision with drainage, or extirpation of

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the entire spleen. These operations have all been tried, but in only a few instances with recovery. The only prospect of success is in the single abscess occurring in the non-embolic cases, as a complication of typhoid or malarial fever, by extension from a local source of infection such as perforating gastric ulcer, the traumatic and idiopathic abscess, etc. The embolic type of abscess should not be interfered with, as a rule, being only a complication of conditions which in themselves are fatal. Otherwise the treatment of abscess of the spleen is purely symptomatic. The comprehensive papers by Lauenstein[1] and Bessel-Hagen[2] on the surgical aspect of abscess of the spleen are recommended for further information.

INFARCT OF THE SPLEEN.

Synonyms.—Embolism of the spleen is frequently used as synonymous with infarction. This use, strictly speaking, is not correct, as embolism is not identical with infarction, but rather the direct cause of infarction. Furthermore, embolism, while the common, is not the exclusive cause of infarction of the spleen, thrombosis also playing a minor etiological role.

Etiology.—Next to the kidney, the spleen is the most frequent site of infarction, due to the fact that the arterial radicles of the spleen and kidney are partly of a type known as "terminal arteries" or "end arteries," *i. e.*, without anastomoses. The most frequent cause of splenic infarction is the conveyance of an embolus from the valves of the left side of the heart in endocarditis to one of the subdivisions of the splenic artery, thus producing occlusion with resulting infarction of the area supplied by the plugged artery. Embolism arising from cardiac thrombi, atheroma or aneurism of the aorta, and pyæmia is also a frequent cause. Thrombosis of the radicles of the splenic artery or vein developing in the specific fevers, such as typhoid fever or in marantic and anæmic states, is not very rare. In exceptional instances the infarction may originate by backward extension of a thrombus in the splenic vein.

Pathology.—The territory supplied by the plugged artery disintegrates by coagulation necrosis, producing a "white infarct" ("anæmic infarct") or, in case of excessive hemorrhage into the area, a "hemorrhagic infarct" of the spleen, consisting of a wedge-shaped area with its base directed toward the surface of the spleen and its apex pointing inward to the site of the embolus. The color of the infarct varies considerably with the nature of the infarct and its age. When fresh it is usually of some shade of yellow or red from the infiltrated blood which surrounds it or extends into it. Later its color fades and it may become almost white. The "white infarct" is from the first of a pale color, more or less tinged with blood. Subsequently the infarct becomes organized and replaced by fibrous tissue, the contraction of which may ultimately leave only a puckering or scar on the surface of the spleen to indicate its site. The organ may thus be considerably deformed by the cicatrization of multiple infarcts. They may be single or, more commonly, multiple and vary from the size of a pea to that of a large orange, according to the size of the artery which is plugged. In case the embolus causing the infarction is infective, as it sometimes is in malignant endo-

[1] *Deutsch. med. Woch.*, 1887, Nr. 51.
[2] *Archiv f. klin. Chir.*, 1900, Band lxii, Nr. 1.

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carditis or pyæmia, the infarct may be converted into an abscess and the spleen may be filled with such abscesses following multiple infarction. When an infarct extends to the surface of the spleen, as it usually does, a circumscribed area of perisplenitis generally results.

Symptoms.—The most reliable symptom is pain developing suddenly in the region of the spleen in the course of valvular disease of the heart, especially malignant endocarditis, or other conditions liable to give rise to embolism. The pain varies in intensity and in some cases may be entirely absent. It is increased by deep respiration or movement. It may last for some days or in exceptional cases for several weeks. Tenderness on pressure and slight swelling of the spleen are the rule. Rigors and fever may occur and, if persistent, indicate infective embolism with probable abscess formation. A peritoneal friction rub is sometimes heard over the spleen, indicating the presence of perisplenitis. The symptomatology of infarct of the spleen is often complicated by that of the disease to which it is secondary.

Diagnosis.—The diagnosis is suggested by the symptoms and signs, above described, occurring in the course of valvular disease of the heart. The diagnosis is made more certain if signs of infarction of the kidney are also found. Infective embolism with secondary abscess formation in the spleen presents the clinical picture of abscess.

Prognosis.—The prognosis is good in simple embolism. In infective embolism it is that of abscess and of the primary disease that gives rise to the embolism.

Treatment.—The treatment is directed chiefly toward the relief of pain by means of local applications of heat or cold, dry cupping, strapping the side with adhesive plaster to limit the respiratory movements, and, if necessary, by the hypodermic use of morphine. Abscess formation requires surgical intervention.

RUPTURE OF THE SPLEEN.

This may be briefly considered because of its medical interest in connection with enlargement of the spleen in malaria, typhoid fever, and other conditions.

Etiology and Pathology.—The causes are traumatism and preëxisting disease of the spleen. Severe traumatism may lead to the rupture of a perfectly healthy spleen, but far more frequently slight traumatism causes rupture of a spleen already diseased. The morbid conditions that most commonly lead to rupture are excessive enlargement and stretching of the capsule, occurring especially in malaria. In addition, the spleen substance may be soft and friable, the capsule extensively diseased so that its normal elasticity is impaired, and adhesions may further render it more liable to injury from slight strain. Spontaneous rupture may occur in such cases, but generally the rupture is caused by slight trauma induced by strain, coughing, etc. In Mauritius, rupture of the malarial spleen is reported as the most frequent cause of sudden death. During a residence of two and a half years in the East Indies, Playfair made twenty autopsies on cases of ruptured malarial spleen. The acute splenic enlargement of typhoid fever, relapsing fever, and the other infectious diseases may likewise lead to rupture. Rupture of the spleen has been observed several times as a complication of

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pregnancy, occurring especially during labor or eclampsia. Infarct and abscess of the spleen, aneurism of the splenic arteries, and a varicose condition of the veins are less frequent causes.

The rupture may be single or multiple, slight or extensive, involving the capsule alone or extending into the parenchyma. Depending upon the extent of the laceration and the involvement of vessels, the hemorrhage may be slight or so profuse as to cause sudden death. In case of extensive adhesions the hemorrhage may take place into them and remain encapsulated. Rarely it is entirely subcapsular. Secondary peritonitis occurs only in case of the discharge of infective material, as from abscess, septic infarct, etc.

Symptoms and Diagnosis.—The occurrence of rupture is indicated by sudden, intense, lancinating pain, with a sensation as though something had torn in the region of the spleen, followed by symptoms of internal hemorrhage with shock—colicky pains, pallor, syncope, faintness; rapid, thready pulse; cold extremities, nausea, vomiting; sighing, rapid respiration; dilated pupils, subnormal temperature, etc. Fever usually follows. The physical examination shows distention of the abdomen, with dulness or fluctuation in the flanks or over the site of the accumulated blood. The size of the spleen, if previously determined, is found reduced. Signs of secondary peritonitis may follow in case the rupture arose from septic infarct or abscess.

The diagnosis is suggested by the morbid condition of the spleen and by the symptoms and signs above described. It may be impossible in case of slight hemorrhage. Differentiation from rupture of hydatid or other cyst or abscess may be difficult, but in these instances the hemorrhage is likely to be slight and in consequence the anæmic symptoms of shock are lacking. Differentiation from internal hemorrhage from other organs may be impossible, but this is of minor importance as immediate operation is indicated in all such conditions, when the site of the hemorrhage will be readily found.

Prognosis.—This is always extremely grave. Few patients survive the accident, although rare instances of spontaneous recovery are recorded. Death may result immediately from hemorrhage, and occurs in a majority of cases within the first twenty-four hours (Vincent). Surgery offers the only hope, and this is slight, due to the danger of a formidable operation in the anæmic, collapsed condition of the patient and to the disease of the spleen that led to the rupture.

Treatment.—Knowing the liability to rupture of greatly enlarged spleens, we should limit our physical examination to the minimum consistent with accuracy and should use only the lightest pressure and percussion in defining the organ. The patient and his attendants also should be warned of the danger of even slight strain. Exploratory puncture for diagnosis is a dangerous procedure and is seldom justifiable, perhaps never in the enormous ague-cake spleen of malaria, which is especially prone to rupture. Death from secondary rupture and hemorrhage has been known to follow exploratory puncture.

The medical treatment is practically hopeless. The patient is confined to bed at absolute rest, all movements are prohibited, hypodermic injections of morphine are given to relieve pain and promote rest, large ice-bags or the ice-water coil are applied over the spleen, and commonly hæmostatic drugs are administered, although it is doubtful whether any of them are of value. The calcium salts, preferably the lactate, may be given in 20 or 30

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grain (1.3 to 2 gm.) doses every three hours to increase the coagulability of the blood, as claimed by Wright. With symptoms of collapse the temperature of the body must be maintained by applying heat, and stimulants must be used with caution. Such measures, however, can be only of trifling value in the presence of so formidable a condition.

Surgery must be considered as offering the only real chance of recovery, slight though it be. The question of surgical intervention in such cases is at present largely theoretical, as but few operations for rupture of the spleen have been performed. Riegner performed splenectomy with recovery in one case of traumatic rupture. Vincent has reported cases of rupture of malarial spleens successfully operated on, although not by extirpation. The kind of operation must be determined by the special conditions presented in each case. In general, splenectomy seems to be the operation of choice, unless contra-indicated by the poor condition of the patient or the serious nature of the morbid process and the condition of the spleen. The question of the limitations of successful surgical intervention must await the experience of the future for determination.

THROMBOSIS OF THE SPLENIC VEIN.

Thrombosis with obliteration of the splenic vein and its radicles is of clinical interest chiefly from the point of view of differential diagnosis, the symptomatology and clinical picture being identical with those of splenic anæmia. Its recognition might also be of practical importance for its relief by means of splenectomy.

Etiology.—Primary thrombosis of the splenic vein and its radicles is rare; it may arise from atheroma and calcification of the walls of the vessel. Secondary thrombosis of the intrasplenic branches is not very uncommon from infarction, abscesses, etc., and the main trunk may be thrombosed as a result of diseases of the pancreas, by various extrinsic processes such as tumors or inflammatory disease, or by backward extension of a thrombosis of the portal and mesenteric veins. Typhoid fever is a rare cause of thrombosis of the splenic vein and its radicles, as in the case reported by Köster. Marantic thrombosis of the splenic veins due to cachectic states may also be considered possible. Twisting of the splenic vein by torsion of the pedicle in movable spleen may lead to thrombosis of the vein with congestion, enlargement, infarction, and extensive necrosis of the spleen, as in a case reported by Osler.

Pathology.—The morbid anatomy is that of the vein itself, either primary or secondary, and the changes in the spleen resulting from the venous obstruction. Congestion and enlargement result except in certain instances where the thrombosis involves exclusively the extrasplenic part of the main trunk, with the development of a collateral venous circulation sufficient to compensate the obstruction; that such a result is exceptional is shown by the fact that splenic congestion and enlargement are the rule in obstruction of the portal vein above the entrance of the splenic vein. The congestion of the spleen leads to the usual changes depending upon this. If the intrasplenic radicles are thrombosed, hemorrhagic infarction results.

Symptoms.—These are entirely due to the mechanical effect of the venous obstruction, namely, enlargement of the spleen and recurring gastric hemor-

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rhage, with their secondary effects. The splenic enlargement may develop rapidly or may be gradual and chronic from the start, depending upon the cause. When the thrombosis involves the main trunk and its intrasplenic radicles as well, the spleen is always congested and greatly enlarged. Thrombosis limited to the extrasplenic part of the splenic vein may be compensated by a collateral venous circulation so that the usual congestion of the spleen is absent or only slight; but this is not the invariable result, as shown by the instructive case described by Bland-Sutton,[1] as follows: "A nurse, twenty-six years of age, suffered for six years from recurring attacks of profuse hæmatemesis associated with a big spleen. The bleeding was attributed to a gastric ulcer, and the amount of the blood she lost in some of the attacks was so great as to reduce the red corpuscles of the blood to 662,000 per cmm. Gradually the corpuscular elements would increase until they reached the proportion of 3,200,000 per cmm. This always indicated that hæmatemesis was imminent and it invariably happened within a few days. The woman herself knew when to expect an attack, and eventually died after a profuse bleeding. At the postmortem examination the splenic vein was large enough to admit the index finger; it contained pouched recesses, and at its junction with the superior mesenteric was blocked by an organized thrombus."

Diagnosis.—The clinical picture is that of splenic anæmia and the differential diagnosis is impossible during life except perhaps by operation.

Treatment.—Splenectomy would be indicated under the same circumstances as in splenic anæmia, chronic splenic tumor, and similar conditions.

AMYLOID SPLEEN.

Synonyms.—Amyloid degeneration of the spleen, lardaceous spleen, waxy spleen, sago spleen.

The description of amyloid disease as one of the primary types of cell degeneration belongs to the field of general pathology, but its special effects upon the spleen may be described in this place as a clinical condition that must be considered in the differential diagnosis of diseases of the spleen.

Etiology.—Broadly considered, the several causes may be included under the heading of a constitutional dyscrasia secondary to chronic cachexias, as only in the rarest instances has the disease been found occurring as an apparently idiopathic process. More specifically, the common causes are chronic suppuration, tuberculosis, and syphilis. Other chronic cachectic conditions, as from nephritis, carcinoma, paludism, leukæmia, gout, plumbism, alcoholism, etc., only exceptionally lead to amyloid disease. Of the common causes, chronic suppuration in its various forms stands preëminent. Even in cases due to tuberculosis or syphilis, secondary infections with ulcerative processes are usually found, although not necessarily. Litten found pulmonary tuberculosis (combined with tuberculous ulceration of the intestines in about one-third of the cases) in 70 per cent. of his cases of amyloid disease. Pulmonary tuberculosis with chronic cavity formation (suppuration) is to-day perhaps the most frequent single cause of amyloid disease. Formerly, before the advent of aseptic surgery, infected wounds,

[1] *Encyclopædia Medica*, vol. xi, p. 335.

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suppuration of bones and joints, and chronic surgical infections in general occupied the first place in the causation. The length of time necessary to the production of amyloid degeneration in the organs has been determined by careful clinical observations as varying from two and a half to six months after the primary cause has begun to operate.

Pathology.—The first recognition of amyloid degeneration of the spleen we owe to Virchow, whose exhaustive investigations carried through many years established the fundamental facts of the process which subsequent studies have only slightly amplified. Amyloid disease of the spleen occurs chiefly in two forms, in which the process involves principally the Malpighian corpuscles, constituting the so-called sago spleen, or the parenchyma of the organ, producing diffuse, parenchymatous, amyloid degeneration. In addition, combinations or variations of these principal forms may occur, leading to a variable picture. The sago spleen shows on section small, pinhead-sized, waxy bodies resembling boiled sago grains in place of the Malpighian corpuscles. The organ is of normal size or slightly enlarged and of somewhat increased consistence. This is the common form of the disease observed in the autopsy room. Parenchymatous amyloid degeneration shows on section a translucent waxy appearance involving more or less completely the parenchyma of the entire organ. The spleen in the early stages may be soft and flabby, but later becomes firm and enlarged, with rounded edge and tensely stretched capsule. Varying degrees of atrophy and fibrosis in the organ are usual. The size of the spleen may be enormous in certain instances. The capsule occasionally shows areas of perisplenitis. The amyloid substance can be demonstrated by suitable chemical reagents.

The spleen is more frequently involved in amyloid disease than any other organ. In Hoffman's statistics of 80 cases of amyloid degeneration, the spleen was involved in 92.5 per cent., the kidneys in 84 per cent., the intestines in 65 per cent., the liver in 62.5 per cent; in Litten's 100 cases the corresponding figures were: spleen, 98; kidneys, 97; intestines, 65; and liver, 63 per cent.

Symptoms.—There are no distinctive symptoms, the only splenic features being the enlargement and its mechanical effects, neither of which are constant. Otherwise the patient's general symptoms are due to the primary disease. Only the large lardaceous spleen resulting from widespread amyloid degeneration of the organ attracts special clinical attention. It may reach enormous dimensions, filling the entire left side and in rare instances extending into the right half of the abdominal cavity. The presenting edge is rounded and the organ feels smooth and hard. Tenderness is not elicited by pressure as a rule. A sense of weight and fulness may be complained of, but actual pain is rare except as a result of rapid enlargement of the organ, with stretching of its capsule or from perisplenitis. Disturbances of function in other organs may be caused by the pressure of the enlarged spleen. Anæmia of considerable grade may be present, but is attributable chiefly to the primary disease or to the functional disturbances of the various organs. The sago spleen is chiefly of pathological interest, as it never reaches a large size.

Diagnosis.—This is suggested when a hard, smooth, splenic tumor is found developing in the course of a chronic disease (suppuration, tuberculosis, syphilis) that is liable to lead to amyloid degeneration, provided the enlargement cannot be better accounted for by some other cause. Symptoms of amyloid disease of the kidneys, intestines, or liver would confirm

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the suspicion and make the diagnosis probable, if not certain. The most important symptoms of amyloid degeneration of these organs are as follows: of the liver, a smooth, firm, painless, marked enlargement; of the intestines, persistent, uncontrollable diarrhœa; of the kidneys, dropsy, a large amount of pale, clear urine of low specific gravity containing usually considerable albumin and globulin with casts. Marked anæmia and pallor occur in most cases, and are due to the primary disease as well as its effects and complications.

Treatment.—This is chiefly that of the primary disease, which must, if possible, be removed as a cause of further degeneration. Syphilis can be cured and chronic suppuration is often amenable to successful surgical treatment. The same is true of certain forms of tuberculosis, *e. g.*, involving the bones, joints, glands, etc. If the cause can be removed, the secondary amyloid disease will stop its further destructive changes in the spleen and other organs. The destruction already accomplished cannot be repaired, but if it has not reached a severe grade its existence may be compatible with a long life. General tonic treatment is indicated for the anæmia and malnutrition. Iron and arsenic may be tried and the syrup of the iodide of iron has been found especially valuable. Fresh air, an abundant nourishing diet, and a change of residence are all of the greatest assistance. Treatment at one of the hot springs, combined at the same time with other suitable measures, may prove of great value, especially in the syphilitic cases. The special symptoms and complications must be treated as they arise.

TUMORS OF THE SPLEEN.

New-growths of all kinds, whether benign or malignant, primary or secondary, are of rare occurrence in the spleen compared with their general frequency in other organs. No satisfactory explanation of this has been offered. The following varieties have been observed:

Benign Tumors.—Fibroma.—A rare condition, occurring as single, sometimes multiple, small, round nodules, about the size of a walnut.

Lymphangioma.—Two cases have been reported by Fink. Both were multiple and extensively invaded the spleen substance, with protrusions on its surface.

Angioma Cavernosum.—Cases have been reported by Birch-Hirschfeld, Förster, Hoge, Homans, and Langhans. Langhans' case was one of pulsating angioma observed during life. The tumors are sometimes of enormous size and they may lead to chronic ascites, characterized by large quantities of a blood-stained fluid. They are believed sometimes to degenerate into serous cysts.

Lymphadenoma.—This has been observed in a few cases in the form of small, single or multiple, circumscribed collections of lymphoid cells, sometimes surrounded by a connective-tissue capsule. They probably represent instances of localized hyperplasia of the Malpighian bodies. Such collections of cells have been mistaken for sarcomata. They should not be confused with the similar lymphomatous collections of leukæmia.

Endothelial Cell Masses.—The proper classification of those rare instances of tumor-like masses of endothelial cells in the spleen, described by Weichselbaum, Gaucher, Bovaird, Stengel, Rolleston, Collier, and Picou and Raymond, is still a matter of opinion. Weichselbaum reported his case as

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"primary multiple endothelial sarcoma of the spleen," although Birch-Hirschfeld, who examined the specimens, regarded the condition as a simple chronic hyperplasia of the normal endothelial cells of the spleen. Gaucher regarded his case as representing a "primary epithelioma of the spleen," although the subject was known to have had an enlarged spleen for twenty-five years. Stengel, who reported a remarkable case showing endothelial cell masses in the spleen resembling true neoplasms, so regarded them. The more general interpretation of these cases, however, is that they are not true neoplasms, but rather a special form of chronic hyperplasia of the endothelial cells, constituting a variety of chronic splenic anæmia. The clinical course agrees with splenic anæmia in every particular.

Malignant Tumors.—Carcinoma.—Primary epithelial growths of the spleen are so rare that their occurrence has been doubted, especially as no epithelial tissue occurs in it normally, although it is theoretically not impossible to conceive of the congenital inclusion of embryonic epithelium. Some of the cases reported as primary are undoutedly secondary, the primary focus having been overlooked. Other cases are instances of sarcoma or of chronic endothelial hyperplasia. Litten found but ten cases reported as primary carcinoma in the literature, and in a majority of these the diagnosis was open to criticism. While, therefore, the possibility of primary carcinoma of the spleen cannot be denied, its proof has not been satisfactorily established.

Secondary metastatic carcinoma of the spleen is also of very infrequent occurrence.

Sarcoma.—While excessively rare, sarcoma is the most important of all forms of primary tumor of the spleen. Cases of primary round-cell sarcoma and lymphosarcoma have been observed. The few authentic cases have occurred chiefly in adult females. One case of congenital sarcoma of the spleen in a child is reported by Clark. Cases of lymphadenoma and endothelial hyperplasia have been mistaken for sarcoma. The growth is usually multiple, consisting of nodules varying in size from a cherry to a hen's egg. The spleen is usually greatly enlarged and its surface may be irregular from the projection of the masses.

The symptoms and signs are: rapid enlargement of the spleen, sometimes with palpable nodules; persistent pain over the spleen, radiating over the abdomen or upward; tenderness on pressure, and the cachexia and general symptoms accompanying malignant growths elsewhere. The clinical diagnosis can never be made with any degree of certainty. As to treatment, it is doubtful whether a single case has thus far been saved by operation, because surgical intervention has been attempted too late and after metastases have already developed.

Secondary sarcoma is relatively less infrequent, but it is remarkable how seldom the spleen is invaded even by metastatic growths.

CYSTS OF THE SPLEEN.

Cysts of the spleen belong to three classes, as follows:

I. **Simple Cysts,** *i. e.*, serous, hemorrhagic, and lymph cysts.

II. **Dermoid Cysts.**

III. **Parasitic Cysts,** *i. e.*, hydatid cyst, Cysticercus cellulosæ, and Pentastomum denticulatum.

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I. **Simple Cysts.**—These, which are comparatively rare, are classified as *serous*, *hemorrhagic* (*blood*), or *lymph cysts*, according as their contents correspond to one or another of these fluids. In other respects they have no essential differences and will be considered together.

The fluid of *serous cysts* is clear, of low specific gravity (1003 to 1010), and non-albuminous. *Hemorrhagic cysts* are characterized by containing considerable blood or blood remnants, the contents varying in color and consistence with the amount of blood, age, alterations, etc. *Lymph cysts* contain a fluid with the characteristics of lymph, *i. e.*, albuminous, of high specific gravity, and with a tendency to spontaneous coagulation when exposed to the air. All three types of cyst always contain cholesterin crystals in varying amount and may undergo degeneration into so-called *cholesterin cysts*, characterized by a fatty detritus loaded with cholesterin crystals. Considerable hemorrhage occurring in serous and lymph cysts converts them essentially into hemorrhagic or blood cysts.

Etiology.—Some of the cysts arising in the capsule of the spleen may be caused by the degeneration of inclusions of peritoneal endothelium (Renggli). Others are caused by degeneration of the Malpighian bodies or spleen pulp or from degenerated lymphangiomas. True retention cysts do not occur, due to the absence of tubular glandular structure, although certain blood and lymph cysts may perhaps arise by occlusion of blood or lymph vessels with ectasis and retention. Trauma and traction exerted by adhesions or disease of vessel walls may lead to hemorrhage, causing hæmatoma which may become encapsulated and converted into a cyst. A serous or lymph cyst may be converted into a blood cyst by hemorrhage. Repeated hemorrhage into a cyst may cause successive enlargements of the cyst. By these various processes simple cysts of the several types may arise, varying in character according to the cause and the structure in which they originate. In general, trauma is the most frequent single cause of cyst formation in the spleen. From trauma blood cysts may develop quite rapidly, reaching their maximum size within a few weeks; in other cases the full size may only be attained after years.

Pathology.—Simple cysts may be single or multiple, unilocular or multilocular, very small or large, sometimes reaching the size of a man's head. They are usually lined by endothelium, although in old cysts this may not be found. They may be situated in any part of the spleen, commonly in the lower anterior part, and especially in or beneath the capsule. Old cysts may have thick, calcified walls. Perisplenic adhesions may form over the site of the cysts. The spleen may be dragged down by the weight of enormous cysts into any part of the abdominal cavity, and it has been found occupying the bony pelvis, as in the case reported by Jakoulieva. Rupture of the cyst or infection of its contents is very rare.

Symptoms.—Small cysts are of no clinical importance, only large cysts leading to symptoms and complications that call for medical attention. The symptoms arising are usually produced mechanically by the traction or pressure of the large cyst. Thus, a feeling of weight or fulness, tenderness, and digestive, urinary, respiratory, or other functional disturbances are common. Actual pain is unusual, except in case of perisplenitis, dislocation of the spleen by traction, rapid stretching of the capsule by large hemorrhages, or other accidental complications. In addition to such common symptoms, the cyst may produce enlargement of the abdomen over its site, and upon palpa-

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tion fluctuation is usually obtained. Suppuration of the cyst, which is rare, produces the symptoms of abscess.

Diagnosis.—This must be based upon the discovery of a fluctuating enlargement definitely arising from the spleen, or by diagnostic puncture or exploratory operation. Fluctuation cannot always be elicited and even puncture may prove negative if the contents are thick. In such cases cyst can only be suspected by the outline of the tumor, and exploratory laparotomy may be required to determine its nature. If a cystic spleen is dislocated into the abdomen, diagnosis may be very difficult or impossible.

In the differential diagnosis, cyst of the left kidney, hydronephrosis, ovarian cyst, and hydatid cyst of the left kidney or left lobe of the liver must be carefully considered. All of these conditions, especially ovarian cyst, have been diagnosed in cases of cyst of the spleen. Other possible sources of confusion are loculated pleural effusion of the left base, cyst of the pancreas, and solid tumors or inflammatory masses in the upper left quadrant of the abdomen. Simple cyst can be differentiated from hydatid cyst only negatively, *i. e.*, by obtaining by puncture fluid free from hydatid elements, which, of course, does not exclude the possibility of the cyst being hydatid. On the other hand, hydatid cyst is proved by finding in the fluid hooklets, scolices, bits of lamellated membrane, etc., or by other evidences of echinococcus disease, such as the discharge of daughter cysts, hooklets, scolices, lamellated membrane by rupture into the bronchi, stomach, intestine, pelvis of the kidney, or externally. Hydatid cyst of the spleen is made probable if cystic disease of the liver can at the same time be determined. Hydatid fremitus is an inconstant and unreliable sign that can be simulated in other conditions. Diagnostic puncture should be made at the bottom of a dependent part of the cyst, in order to increase the chance of obtaining hydatid elements which settle by gravity to the lowest part of the cyst. Puncture should be performed only with a full understanding of its dangers.

Treatment.—A close-fitting abdominal bandage may be worn to support the weight of the cyst, relieve symptoms, and prevent dislocation of the spleen. Surgical intervention is required when the cyst is very large, when it causes marked functional disturbances and troublesome symptoms, when it becomes infected, when the spleen is dislocated into the abdominal cavity, and in the presence of other serious complications. Splenectomy and partial resection of the spleen are the only operations advocated by modern authorities. Bessel-Hagen,[1] in 1900, collected 7 cases of small hemorrhagic cysts of the spleen, all operated on by splenectomy with recovery. Filippow and Kusnezow,[2] in 1891, reported 7 cases of large cysts of the spleen that were operated upon, 5 by splenectomy and 2 by partial resection, all with cure, to which Litten[3] adds 2 other cases from the literature cured by resection, making 9 cases of large cyst operated on, all with cure.

II. **Dermoid Cysts.**—These are of the rarest occurrence in the spleen, and because of their deep situation in the organ and small size are only of pathological interest.

III. **Parasitic Cysts.** (*a*) **Hydatid Cysts.**—Hydatid or echinococcus cysts of the spleen occur in about 3 or 3½ per cent. of all cases of hydatid disease (Litten). Hirschberg, in 1888, found in the literature 41 cases of primary

[1] *Archiv f. klin. Chir.*, 1900, Band lxii, Nr. 1.
[2] *Centralbl. f. Chir.*, 1891.
[3] *Nothnagel's Encyclopædia.*

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echinococcus cyst of the spleen and 37 cases in which the spleen and other organs were involved. In the statistics of the disease in North America collected by the writer,[1] in 1901, among 241 cases, 9 instances of involvement of the spleen were found (3.7 per cent.).

Hydatid cyst of the spleen is always unilocular and usually single, but exceptionally more than one cyst may be found. The cysts may occupy any portion of the organ and may reach a large size. Occasionally hydatid cysts develop not in the spleen proper, but in the gastrosplenic omentum, involving the spleen secondarily by extension.

Hydatid disease of the spleen follows the same course characteristic of it elsewhere. The symptoms are similar to those of simple cyst. Inflammation of the cyst is liable to occur, in case of which the symptoms are those of abscess. The differential diagnosis from simple cyst has been considered above. Diagnostic puncture and exploratory laparotomy are the chief means. Diagnostic puncture is not devoid of danger when performed on hydatid cysts. It may be followed by serious symptoms of toxæmia, sometimes resulting in death, may lead to fatal general peritonitis if the cyst is infected, and may permit the escape of living hydatid elements capable of disseminating the disease in the peritoneal cavity. While such sequelæ are fortunately not common, they should be considered possible and exploratory puncture should be restricted to exceptional cases. If an exploratory operation is warranted, preliminary puncture through the abdominal wall should never be practised. The differential diagnosis of hydatid cyst of the spleen must be made from the same conditions as in simple cyst of the spleen.

The *prognosis* is always grave when the cyst is large or reaches the surface of the spleen, because of its tendency to rupture. Destruction of small hydatid cysts may occur with calcification, as proved by autopsy findings.

The *treatment* is strictly surgical, either by extirpation or incision. Total splenectomy is the operation of choice, unless contra-indicated.

(*b*) **Cysticercus Cellulosæ and** (*c*) **Pentastomum Denticulatum.**—Each of these parasitic cysts has been found in the spleen in rare instances. They consist of small cystic bodies that may become obliterated and calcified. They never produce clinical symptoms and are of pathological interest only.

SPLENIC ANÆMIA.

Synonyms.—Anæmia splenica, the splenic form of pseudoleukæmia or of Hodgkin's disease, primary or primitive splenomegaly, endothelial hyperplasia of the spleen, splenomegalic cirrhosis of the liver, Banti's disease, etc.

Definition.—A disease, probably an intoxication of unknown nature, characterized by great chronicity, primary progressive enlargement of the spleen which cannot be correlated with any known cause (primary splenomegaly), anæmia of a secondary type with leukopænia, a marked tendency to hemorrhage, particularly from the stomach, and in many cases a terminal stage with cirrhosis of the liver, ascites, and jaundice (Banti's disease). This definition, adopted from Osler, covers the main features of a disease picture that has only in recent years come into prominence and been recognized as probably representing a well-defined disease. Previously great confusion

[1] *American Journal of the Medical Sciences*, January, 1902

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had existed in the classification, and it cannot be claimed that our present understanding permits of any exactness. The present attempt at classification must be regarded rather as tentative, pending further investigation and the solution of the question of specific cause. Many observers believe that the group of cases now included under the name of splenic anæmia, as defined above, will ultimately be resolved into subdivisions of separate and distinct etiology. The name "splenic anæmia" is therefore used at present as covering a certain group of cases with a fairly definite symptom-complex that cannot be explained by any known cause. It is now generally believed, however, that this symptom-complex, while probably including many cases of different nature, still, after the exclusion of all such cases, represents a large residuum of cases of specific etiology. And to this theoretical residuum of cases, then, the term "splenic anæmia" should ultimately be restricted.

The proposition advanced by Osler and now widely accepted, that "the conditions separately described in the literature as primitive splenomegaly, splenic anæmia, splenomegalic cirrhosis of the liver, or Banti's disease, are stages of one and the same malady," is tentatively assumed by the writer. On this assumption, primary splenomegaly and splenomegaly with cirrhosis of the liver (Banti's disease) are regarded as initial and terminal stages respectively of splenic anæmia.

Historical.—The term "anæmia splenica" was employed first by Griesinger and his assistant, Gretsel,[1] in 1866, for cases of anæmia with chronic splenic enlargement supposed to represent a splenic form of pseudoleukæmia. The first systematic description of the disease was published by Banti[2] in 1883, who reported 3 cases, 2 with autopsies, under the title of "anæmia splenica," though he believed the disease a splenic form of pseudoleukæmia. Banti's paper was published in Italian and remained almost overlooked for years. After this several writers reported isolated cases, evidently of this disease, under a variety of designations. In 1891, Bruhl[3] collected the previously reported cases, 14 in number, and suggested the name "splénomégalie primitive." In 1894, Banti[4] described in French and German journals the form of the disease characterized by splenomegaly with cirrhosis of the liver, to which subsequent writers have attached his name (Banti's disease). In 1900 and again in 1902, Osler[5] brought the subject up to date in very thorough reviews, adding careful notes of 15 cases of his own, a larger number than had been reported by any other writer. These papers, more than those of any other, served to clear away the previous confusion and to more definitely correlate the different types of the disease as different stages of a single morbid entity. For the earlier literature the reader is referred to the critical reviews by Sippy[6] in 1899 and Wentworth[7] in 1901.

Etiology.—The cause is unknown. Bacteriological examination of the organs, cultures, and animal inoculation have all proved negative. A history

[1] *Berl. klin. Woch.*, 1866. [2] *Arch. d. Scuola d. Anat. patol.*, Firenze, 1883, ii, 53.
[3] *Gaz. d. hóp.*, Paris, 1891, lxiv, 241; *Arch. gén. de méd.*, Paris, 1891, i, 673, and ii, 160.
[4] *Semaine méd.*, Paris, 1894, xiv, 318; *Beiträge z. pathol. Anat. u. z. allgem. Pathol.*, Band xxiv, Heft 1, 21.
[5] *American Journal of the Medical Sciences*, January, 1900; *Transactions of the Association of American Physicians*, 1902.
[6] *American Journal of the Medical Sciences*, November, 1899.
[7] *Boston Medical and Surgical Journal*, 1901.

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of malaria occurs in some cases and may be of significance in special forms presenting the symptom-complex of splenic anæmia, but malaria can be excluded as having any necessary relation to splenic anæmia. The course of the disease and the fibrosis of the organs suggest a chronic intoxication, but this is only conjectural. The enlargement of the spleen precedes the anæmia, suggesting that the latter may be derived from some cause originating within the diseased spleen. Another point favoring the theory of a splenic origin of the malady is the results of splenectomy, which seems to have led to great improvement if not to actual recovery in many cases. But such cases must be subjected to a closer scrutiny in diagnosis and a longer test as to the durability of the first improvement than has heretofore been done before this argument can carry great weight, for it is well known that the removal of any greatly enlarged spleen, when clearly secondary to debilitating diseases such as syphilis, malaria, etc., may be followed by marked improvement and disappearance of all symptoms, including the anæmia. Dock and Warthin[1] suggest that the anæmia may be caused by an excess of hæmolysis occurring in the newly formed hæmolymph glands over that of the normal spleen or to a disturbance in the elaboration of the products of blood destruction. But all such arguments, suggestive as they undoubtedly are, fail to account for the primary changes in the spleen. Perhaps the fibrosis of the spleen, the anæmia, and the final cirrhosis of the liver may all be due to a common cause, an intoxication of unknown nature. The order of development of the principal morbid changes would not seem to weigh against such an assumption. Even although it be granted, however, that the spleen is the organ that is primarily affected by a cause of unknown nature, it is still possible, if not probable, considering the apparent benefit resulting from splenectomy, to look upon the disordered and diseased spleen as secondarily involved in causing the subsequent changes that ultimately develop in other organs. Some such view seems to be the prevalent one and finds its chief support in the claim that splenectomy results in a radical cure of the disease. This claim, however, cannot be accepted as yet proved by the meagre statistics of the results of splenectomy.

Incidence.—The disease, a few years ago supposed to be rare, is not very infrequent, judging from the recent reports since attention has been directed to it. The writer has seen 8 cases in the last nine years and Osler has reported 15 cases as seen within ten years. The cases are widely distributed, with no special geographical or racial incidence. *Sex:* A large majority of the reported cases have been in males, 13 of Osler's 15 cases, 19 of West's collection of 24 cases, and 7 of the writer's 8 cases. *Age:* The age incidence in Osler's series was from twenty to fifty-eight years, in West's collection from nine to seventy-two years, the majority occurring in the middle period of life. Cases beginning in childhood and running a chronic course over many years and presenting the typical clinical and pathological picture are not very infrequent, although cases in infancy and childhood belong to a group that is still very much confused. A *family incidence* has been noted by several writers, Brill, Bovaird, Collier, Wilson, etc., although this seems to be unusual.

Pathology.—Briefly summarized, the essential pathology consists of hyperplasia and fibrosis of the spleen, anæmia of a secondary type, and cirrhosis of the liver as a terminal development in certain cases (Banti's disease).

[1] *American Journal of the Medical Sciences*, January, 1904.

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Spleen.—The enlarged spleen shows a general hyperplastic fibrosis of varying degree involving the capsule, the reticulum of the pulp, and in particular the Malpighian bodies. The pulp and Malpighian bodies are more or less sclerosed and atrophied and often the fibrous Malpighian bodies show hyaline degeneration. The pulp sinuses or blood spaces in many cases show varying grades of hyperplasia of the lining endothelial cells. Areas of hemorrhage, perisplenic adhesions, and infarcts are occasionally found. The characteristic lymphoid infiltration of Hodgkin's disease is never found.

A few cases, presenting all the clinical features of splenic anæmia, including the chronicity, show a special and peculiar change in the spleen, characterized by nests or masses of large, clear, multinuclear endothelial cells, with occasional giant cells. Such cell masses may fill almost the entire organ and cause nodular elevations on its surface varying in size up to several centimeters in diameter, as in a remarkable case reported by Stengel. Between and surrounding these masses the organ is occupied largely by coarse connective tissue. The cell masses appear to originate by the proliferation of the lining endothelial cells of the sinuses. Similar collections of endothelial cells have been found in the mesenteric and regional lymph nodes about the spleen and in the liver (Bovaird).

Weichselbaum,[1] in 1881, first reported a case of this remarkable condition as primary multiple endothelial sarcoma of the spleen ("primares multiplen endothelsarkom des milz"). Gaucher,[2] in 1882, reported a case as primary epithelioma of the spleen ("epithelioma primitif de la rate"), although the spleen of his patient had been enlarged for twenty-five years. Similar cases have been reported by Collier, Picou and Raymond, Bovaird, Stengel, Rolleston, and others.

The relation of these rare cases to splenic anæmia may be considered as undetermined. As already stated, they present all the clinical characteristics of splenic anæmia and a differentiation during life would be impossible except by operation. Provisionally they have been included as a special variety of splenic anæmia, following the rule of most recent writers. That such cases present a striking resemblance to true neoplasms is admitted by all, and several writers have so regarded them, but the majority of recent observers have inclined to the view that these structures represent an endothelial hyperplasia rather than a true neoplastic growth. The long duration of the splenic enlargement, thirteen and twenty-five years, respectively, in Bovaird's and Gaucher's cases, and the fact, as pointed out by Bovaird, that after all these years "the organ is still a spleen," weigh strongly against the neoplastic theory. The relation of such endothelial hyperplasia to the process of fibrosis has been disputed, Bovaird holding that the former develops ultimately into the latter condition, while Stengel dissents from this view. Rolleston suggests that both may develop concomitantly and arise from the same cause, namely, a chronic intoxication. It should be remembered in this connection that, apart from this peculiar type of case, with large, tumor-like masses of endothelial cells, the more common forms of splenic anæmia often show varying degrees of endothelial proliferation in the pulp spaces, and that these proliferated endothelial cells apparently take part in the formation of the new fibrous tissue, as concluded by Dock and Warthin in a careful study of two cases. For a fuller discussion of this phase of the subject the reader is referred

[1] *Thèse de Paris*, 1882.

[2] *Virch. Arch.*, 1881, Band lxxxv, 562.

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to the papers by Bovaird,[1] Harris and Herzog,[2] and Stengel.[3] The variable degree of fibrosis and endothelial hyperplasia of the spleen found in different cases probably depends, in part at least, upon the age of the process.

Liver.—The liver shows no characteristic changes except in the infrequent cases presenting the symptom-complex described by Banti and now generally regarded as a terminal stage of splenic anæmia. In such cases varying degrees of atrophic interlobular cirrhosis occur with reduction in the size of the organ, as in the cirrhosis due to alcoholism. The slight enlargement of the liver commonly observed in the ordinary cases of splenic anæmia is caused by chronic passive congestion.

Veins of the Portal System.—As originally described by Banti and recently by Dock and Warthin, some of the cases may show calcification and stenosis of the veins of the portal system, more particularly the portal and splenic veins, although the mesenteric veins may sometimes be involved. Thrombosis of these veins may also occur and by organization cause complete obliteration of their circulation.

Lymph Glands.—The lymph glands are not enlarged to any extent and show none of the changes characteristic of Hodgkin's disease. According to Dock and Warthin, there is a new formation of small hæmolymph nodes, especially in the mesenteric fat, with deposit of blood-pigment, giving evidence of excessive hæmolysis.

Bone-marrow.—The bone-marrow may show the compensatory changes secondary to any severe anæmia, *i. e.*, proliferation of the erythroblastic tissue. The changes elsewhere may be regarded as accidental or secondary.

Symptoms.—Chronicity.—A special feature of the disease is its remarkable chronicity, dating from the discovery of splenic enlargement. Of Osler's 15 cases, 7 had a duration of more than ten years, 11 more than four years. In 10 of the 26 cases reported by Osler as observed by members of the Association of American Physicians, the disease had lasted more than five years. James and Gaucher have each observed cases lasting twenty-five years. Cases running a more acute course are reported, and West even states that "the disease is not of long duration, from six months to two years, rarely longer," but, as he subsequently says, "the nature of these rapid cases is somewhat doubtful."

Splenomegaly.—The spleen is enlarged, as a rule, to a size rarely attained in any other disease except leukæmia. It usually reaches the navel and often the anterior superior spine of the ilium and it may even pass the median line and occupy a considerable part of the right side of the abdomen. The average weight in 12 cases collected by Rolleston was sixty-one ounces. In Bovaird's case the spleen weighed twelve and one-half pounds. The organ feels smooth and firm and preserves its characteristic form, with its sharp edge and notches presenting anteriorly. The enlarged spleen causes very little pain except when perisplenitis or infarct occurs. Some tenderness on pressure and a certain discomfort of fulness or weight may be complained of. The splenic enlargement is the first development in the disease and may last for years before anæmia appears.

Anæmia.—This follows but never precedes the splenic enlargement, a sequence that has been observed in many reported cases. For years with

[1] *American Journal of the Medical Sciences*, October, 1900.
[2] *Annals of Surgery*, 1901, xxxiv, 111.
[3] *American Journal of the Medical Sciences*, September, 1904.

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marked enlargement of the spleen there may be no anæmia or only a slight reduction of the hæmoglobin. In fact, too much prominence has been given to the anæmia by writers and especially so in the designation of the affection as splenic anæmia. Confusion of cases of pernicious anæmia associated with great enlargement of the spleen with splenic anæmia has added to the undue emphasis of the anæmia. Sooner or later, however, anæmia develops and persists, intensified in certain cases periodically by loss of blood from hæmatemesis, from which the tendency to restoration is impaired and delayed.

The anæmia is of the secondary type and the blood picture presents nothing distinctive. In Osler's series the red corpuscles averaged 3,425,000, with extremes of 2,187,000 and 5,200,000 per cmm. (the latter case showing only 75 per cent. of hæmoglobin). The loss of hæmoglobin is proportionately much greater than that of the red corpuscles and is pronounced, as a rule. In Osler's series the hæmoglobin averaged 47 per cent., with extremes of 25 and 75 per cent. Poikilocytosis is rare and nucleated red corpuscles (normoblasts) are seen only occasionally in the advanced stages of the disease. The *leukocytes* show a marked reduction, as a rule. In the uncomplicated cases of Osler's series the average count was 3850 per cmm. and only 1 case, admitted to the hospital shortly after a profuse hemorrhage, showed a count as high as 12,500. In rare cases a moderate and persistent leukocytosis has been observed, but such cases are exceptional and the presence of leukocytosis in the absence of complications should raise a question of doubt in the diagnosis. The differential leukocyte count shows nothing characteristic. A relative lymphocytosis is sometimes observed.

Hæmatemesis.—As pointed out by Osler, gastric hemorrhage is a special feature of the disease, occurring in 8 of his 15 cases and in 7 of 19 cases observed by members of the Association of American Physicians. In most cases the hemorrhage is due to mechanical causes related to the enlarged spleen and not necessarily to cirrhosis of the liver. The bleeding may come from congestion and diapedesis of the gastric mucosa, from gastric erosions, or from rupture of varicose veins of the œsophagus. The bleeding is profuse and may recur at intervals over a long period of years. In a case seen by the writer quarts of blood had been vomited at intervals of about a year over a period of eleven years.

Other forms of hemorrhage may occur, especially in the advanced stages with anæmia, such as epistaxis and oozing from the gums, which are common, and more rarely retinal hemorrhages, ecchymoses in the skin, or bleeding from other organs.

Pigmentation of the Skin.—A diffuse bronzing or, in some cases, a peculiar steel-gray discoloration of the skin has been observed in a considerable minority of the reported cases, rarely so extreme as to suggest Addison's disease. In a few cases the pigmentation has been patchy and intensified by an accompanying leukoderma. As suggested by West, the pigmentation in many cases may be arsenical, as arsenic is prescribed and used over a long period in most of the cases.

Ascites.—This may occur in the last stage with cirrhosis of the liver (Banti's disease) and also in some cases where cirrhosis of the liver can be excluded by operation or autopsy. In the latter cases the ascites is probably caused by the enlarged spleen in association with anæmia.

Œdema of the ankles may be an occasional symptom in cases with considerable anæmia or with ascites.

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Jaundice.—Jaundice, moderate in degree, occurs occasionally either in association with cirrhosis of the liver or independently of such association, related to circulatory disturbances arising from the enlargement of the spleen, or from pressure by the spleen. The *liver* is of normal size in most cases. Frequently, however, it is slightly enlarged so that its edge can be felt an inch or two below the ribs. With terminal cirrhosis the organ may be contracted and reduced in size.

Digestive disturbances, especially loss of appetite and constipation, less frequently attacks of vomiting, diarrhœa, colic, etc., may occur, although they are not very prominent features in the general run of cases.

The *heart* may show the signs common to all forms of pronounced anæmia, *e. g.*, hæmic murmurs, palpitation on exertion, dilatation, etc.

The *urine* may show traces of albumin and in rare cases nephritis has been described.

The *temperature* is usually normal throughout the disease, but occasional exceptions occur. In the advanced stages there may be a tendency to an afternoon rise of temperature to 100° or higher, and in rare cases it may be irregular or of a hectic type without known complications to account for it. The temperature in such cases has been compared with that frequently observed in other severe anæmias.

Course and Prognosis.—The course of the disease may extend over many years, the patient enjoying fair health and being able to pursue his occupation until the more serious symptoms arise. Periods of improvement or of aggravation of symptoms may occur from time to time, but the tendency is to a slow progressive development of the disease. Death results from progressive asthenia, cardiac syncope, hemorrhage, or intercurrent infection.

Diagnosis.—After what has preceded in the description of the limitations of our understanding of this very complicated group of cases, it will be readily appreciated that a diagnosis should never be undertaken without due consideration of the many possible sources of error, and even then it is only tentative, never quite certain. Early diagnosis is manifestly impossible; later, when the splenic enlargement is associated with anæmia, the diagnosis is probable only after excluding every other cause. The failures of the most eminent clinicians and the revelations of the autopsy-room should be sufficient warning to the less experienced. The conditions that need careful consideration may be grouped as follows:

I. **Splenomegaly without Anæmia.**—This includes a large group of cases due to a great variety of causes, known or unknown, evident or obscure. Certain of these cases represent the primary stage of splenic anæmia, but the diagnosis can never be made in this stage. Some of them continue indefinitely without the development of anæmia or other special features, and may be regarded as simple primary splenomegaly so far as we can determine even after autopsy. Most of such cases, however, are clearly secondary to preceding diseases.

II. **Splenomegaly with Anæmia.**—This includes cases in which the splenomegaly and the anæmia are dependent upon (1) splenic anæmia; (2) various infectious processes, such as syphilis, tuberculosis, malaria, uncinariasis, kala-azar, malignant endocarditis, septicæmia, etc.; (3) diseases of unknown etiology, such as pernicious anæmia, leukæmia, rickets, etc.; (4) new-growths, primary or secondary; (5) mechanical obstructions to the portal circulation, as cirrhosis of the liver, heart disease, thrombosis, sclerosis

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or calcification of the portal or splenic vein, obstructions to these veins by pressure from surrounding structures, such as tumors, inflammatory adhesions, etc.; and (6) special causes operative in infancy and early childhood, producing a group of cases with enlarged spleen and anæmia that cannot be classified in the present state of our knowledge. From all these conditions splenic anæmia must be differentiated. Only the more likely sources of error will be discussed.

Leukæmia.—This is excluded by the absence of its characteristic blood picture, except in rare cases of so-called aleukæmic leukæmia with intermissions of the leukæmic state of the blood.

Hodgkin's Disease.—There is no evidence that a special splenic form of this disease without involvement of the lymph glands occurs, although slight or moderate splenic enlargement is common in association with the enlarged lymph glands. The absence of marked glandular enlargement would seem to differentiate splenic anæmia from cases of Hodgkin's disease showing considerable enlargement of the spleen. As much confusion on this subject has existed, it may be stated that most modern authorities agree that there is no real relation between Hodgkin's disease and splenic anæmia.

Pernicious Anæmia.—While it is a fact that the splenic enlargement sometimes occurring in pernicious anæmia is usually slight, it must also be recognized that exceptional cases occur in which the spleen may attain a size comparable to that of splenic anæmia. The writer has seen three such cases in each of which the diagnosis of splenic anæmia had been made by competent clinicians, basing their opinion upon the great size of the spleen in spite of the presence of a blood picture typical of pernicious anæmia. It is doubtful whether splenic anæmia ever exhibits the extreme degree of anæmia or the other blood changes which together constitute the blood picture pathognomonic of pernicious anæmia. Osler's case No. XIII illustrates this point very well, having been reported in his first series of cases (1900) as one of splenic anæmia, but subsequently withdrawn in his second series (1902) after autopsy as probably a case of pernicious anæmia. The blood of this case was typical of pernicious anæmia, showing 1,380,000 red corpuscles and 3250 leukocytes per cmm., 20 per cent. of hæmoglobin, very marked poikilocytosis, 1.25 per cent. of myelocytes, over 600 nucleated red corpuscles per cmm., of which 72 per cent. were megaloblasts and intermediates and only 28 per cent. normoblasts. As this case has been utilized by many recent writers as a basis for the description of the blood changes in advanced cases of splenic anæmia, the error arising therefrom should be emphasized. Several similar cases have since been reported as splenic anæmia, but the diagnosis in all such cases is doubtful or more probably pernicious anæmia.

As favoring a diagnosis of splenic anæmia as against pernicious anæmia in such doubtful cases, a relatively greater reduction of hæmoglobin than of red corpuscles and a failure to find megaloblasts have been mentioned as decisive; but, in fact, such points are quite incompetent for a decision, as both occur frequently in cases of pernicious anæmia. The point, then, should be strongly emphasized that pernicious anæmia may in rare cases be associated with great splenic enlargement, the spleen reaching the level of the umbilicus or even the pelvic bones, and such enlargement should not be regarded as excluding pernicious anæmia or as demanding a diagnosis of splenic anæmia. As already stated, it is doubtful whether splenic anæmia ever attains the extreme anæmia common in pernicious anæmia, and it is safer at present to

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regard cases presenting such extreme grades of anæmia with enormous spleens as cases of pernicious anæmia.

Cirrhosis of the Liver.—Several types of hepatic cirrhosis with splenic enlargement occur which are liable to be mistaken for splenic anæmia, as follows:

1. *Syphilitic Cirrhosis of the Liver.*—Syphilis of the liver, whether congenital or acquired, may lead to splenic enlargement, not as a rule great, although in rare cases the spleen may fill the whole left side of the abdomen, as in a patient recently under observation by the writer. The liver in such cases is usually irregularly enlarged, a most important differential point. Later the liver may be contracted and reduced in size. There may be considerable anæmia, jaundice, ascites, hæmatemesis, etc., all suggesting a late stage of splenic anæmia (Banti's disease). A persistent leukocytosis occurs in certain cases, a point seldom seen in splenic anæmia in adults. A definite history of syphilis, other evidences of syphilis, or improvement under treatment by mercury and iodide may clear up the diagnosis.

2. *Atrophic Cirrhosis of the Liver.*—The alcoholic form of cirrhosis often presents enlargement of the spleen, slight or moderate as a rule, but exceptionally enormous. Differentiation from splenic anæmia must be based on the history of alcoholism, the absence of much anæmia except in the terminal stage or after profuse hemorrhage, the reduced size of the liver, the hepatic facies, the history of the late development of the splenic enlargement subsequent to the hepatic symptoms, and a general consideration of the case in its history and all its features. Banti's late stage of splenic anæmia with cirrhosis of the liver, ascites, jaundice, etc., may be impossible of differentiation from primary cirrhosis of the liver with secondary splenic enlargement except by the absence of a history of alcoholism and the knowledge that the splenic enlargement had existed for a long time prior to the development of signs of cirrhosis of the liver.

3. *Hypertrophic Cirrhosis of the Liver* (*Hanot's Cirrhosis*).—This disease, occurring mostly in young people, is characterized by a very chronic and marked enlargement of the liver, considerable enlargement of the spleen, chronic icterus of varying degree, a hemorrhagic tendency, and sometimes by leukocytosis, fever, etc. The great size of the liver, firm and smooth, the long duration of this enlargement, the chronic jaundice, and the general prominence of the hepatic and biliary symptoms serve to differentiate the affection from splenic anæmia. The splenic enlargement is also less marked, although the writer has seen one patient in whom the spleen reached below the navel.

4. *Hæmochromatosis.*—This rare type of hypertrophic cirrhosis of the liver is characterized by chronicity, the deposit of an iron-containing pigment in the organs and skin leading to the production of sclerosis of the liver, spleen, and pancreas, with great enlargement of the liver and to a less extent of the spleen, bronzing of the skin, and, as a terminal event, diabetes. The hepatic and splenic enlargement develop progressively at the same time. A slight anæmia may also occur. These cases must be recognized and carefully differentiated from splenic anæmia.

5. *Cirrhosis of the Liver with Splenomegaly in Infancy and Early Childhood.*—This includes a very large and complicated group of cases that are still confused and little understood. Anæmia is usually but not invariably associated. Cirrhosis of the liver is also not invariable. Ascites, jaundice,

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and hemorrhages from the stomach may occur. A family form of splenomegaly in infancy or early childhood occurring in several members of a family is recognized and may belong to this general, ill-defined group. Many cases are clearly secondary to such conditions as rickets, syphilis, scurvy, marasmus, etc., but others occur without evident cause. The subsequent history and course of certain of these cases make it probable that they are cases of chronic splenic anæmia, as seen in adults, but a diagnosis of splenic anæmia in infancy or early childhood is hazardous.

6. *Splenomegalic Cirrhosis of the Liver.*—This is cirrhosis of the liver developing subsequently, and perhaps secondarily, to primary enlargement of the spleen. As previously explained, this association is now generally believed to represent the terminal stage of splenic anæmia (Banti's disease). It is indicated clinically by the development of cirrhotic symptoms, namely, ascites, jaundice, hemorrhages from the stomach, etc. Such symptoms, however, developing in the course of splenic anæmia, do not necessarily indicate cirrhosis of the liver, as any of them may occur without the slightest trace of cirrhosis.

Splenomegaly from Portal Obstruction.—As already described, the complete picture of splenic anæmia may be caused by obstruction of the portal or splenic vein, the obstruction arising within or outside of the vessel. Several such cases are recorded. The differentiation from splenic anæmia during life is usually out of the question, and even after autopsy it may be impossible to determine the sequence, *i. e.*, whether the portal obstruction caused the splenomegaly or the disease of the spleen led to thrombosis or sclerosis of the vein.

Chronic Splenitis in the Infectious Diseases.—The enlarged spleen secondary to certain chronic infectious diseases, such as malaria, syphilis, tuberculosis, uncinariasis, kala-azar, malignant endocarditis, etc., requires careful differentiation from splenic anæmia. Errors may arise from any of these conditions. Syphilis and malaria in particular have led to many mistakes. The writer has known a case of multiple infarcts of the spleen, arising from chronic endocarditis and characterized by great splenic enlargement and anæmia, to be mistaken for splenic anæmia.

Amyloid Spleen.—The large, lardaceous spleen is always secondary to chronic syphilis, tuberculosis, suppurative processes in the body, etc., and the diagnosis is suggested by the presence of one of these conditions, usually in association with evidences of amyloid disease of other organs,

Malignant Disease of the Spleen.—Primary carcinoma and sarcoma of the spleen are so rare that their existence has been doubted. Secondary malignant disease of the spleen is also infrequent. It is suggested by the existence of the disease in other organs, an enlarged spleen with irregularities on its surface, cachexia, wasting, leukocytosis, fever, etc.

Tumor of the Left Kidney.—The writer witnessed a laparotomy performed for supposed splenic anæmia in which malignant disease of the left kidney caused an enormous abdominal tumor simulating an enlarged spleen. A point of some diagnostic value in distinguishing large malignant growths of the kidney or inflammatory mass involving the kidney from enlargement of the spleen is the usual presence of leukocytosis in the former conditions and its absence in splenic enlargement.

Gastric Ulcer.—The recurring hemorrhages of splenic anæmia suggest gastric ulcer as a cause. The first case of splenic anæmia ever seen by

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the writer was diagnosed as gastric ulcer by an eminent authority. The enlarged spleen and other features of splenic anæmia should serve to differentiate, although it is possible for the two conditions to co-exist.

Treatment.—General.—The medical treatment is purely symptomatic; symptoms and complications must be treated on general principles. For the anæmia, iron and arsenic may be tried, with rest, fresh air, abundant feeding, etc. Many cases are reported as improved by such simple measures, but in general the favorable effects are only slight and temporary.

X-ray Treatment.—The application of the *x*-rays over the spleen has been tried with some degree of success. The effect on the splenic enlargement in some cases has been marked and associated symptoms have been more or less relieved. The improvement, however, has not, as a rule, been permanent, and the general tendency at present is to regard the use of the *x*-rays as more palliative than curative. It is fair to state, however, that final conclusions as to this treatment must await further experience.

Surgical Treatment.—*Splenectomy.*—Surgical treatment seems more promising. As originally advocated by Banti, splenectomy has been practised in a considerable number of cases in recent years. The hope of a radical cure by splenectomy was suggested by theoretical considerations of the supposed essential part played by the diseased spleen in leading to the development of the various changes in the advanced stages. From the practical standpoint, the nature of the primary cause of the disturbance of the spleen may be disregarded. The vital question is whether the spleen, involved in a morbid process, by reason of some defect of function, causes the grave secondary changes in other organs If so, the operation of splenectomy should be entertained as either palliative or curative.

The enlarged spleen may act as the essential and sole cause of subsequent changes or merely as a secondary and partial factor in causing the other disturbances. If it acts as the sole and essential cause, splenectomy would clearly be indicated as early as the diagnosis could be made. If, on the other hand, the enlarged and disordered spleen acts merely as a subordinate and partial factor, splenectomy would not be indicated except for the relief of actual distressing symptoms, as recurrent profuse hæmatemesis, pressure effects, etc.

As pointed out, marked improvement has resulted from excision of the enlarged spleen in various anæmic states clearly secondary to general infectious diseases, *e. g.*, malaria, syphilis, etc. Splenectomy may, therefore, be of value and indicated for the relief of symptoms irrespectively of whether the spleen plays an exclusive, essential, etiological part or not. So also in splenic anæmia, splenectomy might at least be expected to cause the relief of certain symptoms and to improve the general condition.

Hence two different points of view might be held with respect to the indications for splenectomy in splenic anæmia, the one with the expectation of a radical and permanent cure, the other with the object of the removal of special symptoms and the improvement of the general condition of the patient. This distinction should be appreciated clearly and future reports of the results following successful splenectomy for splenic anæmia should be made more explicit in the details, extent, and permanency of the improvement. In the end the result of experience alone can determine the exact indications for the operation.

The available statistics of the results of the operation are shown as follows:

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Harris and Herzog,[1] in 1901, reported from the literature 19 cases belonging to this group in which splenectomy had been performed, "with 14 recoveries, 4 deaths, and 1 case where the result is not stated." Armstrong,[2] in 1906, brought the statistics down to date with a report of 32 cases operated on by splenectomy, with 23 recoveries and 9 deaths, a mortality of 28 per cent. The weight of the excised spleen in 15 of these cases was stated, as follows: smallest, 790 grams; largest, 5670 grams; average, 1883 grams. In general, in the cases that survived the operation "the patients are reported as being practically restored to health." The anæmia, asthenia, enlargement of the liver, hæmatemesis, jaundice, pigmentation, etc., gradually disappeared in nearly all cases.

As to the permanency of the recovery, only meagre data are available. In 9 cases in Armstrong's collection the patients were reported as well after varying intervals subsequent to operation, as follows: One case each after intervals, respectively, of eight months, nine months, twenty months, twenty-one months, thirty months, thirty-three months, six and a half years, seven years, and eight years. Even in advanced cases with cirrhosis of the liver and ascites, marked improvement following splenectomy has been noted, as in a case reported by Jaffé.[3] Recovery is sometimes retarded, as in Lespeyres' case, in which cachexia and anæmia persisted five months after operation.

It must be admitted, in view of the above statistics, that at present the evidence favors splenectomy as offering the best chance for arresting the progress of the disease and perhaps for establishing a complete cure. Whether the improvement resulting from splenectomy can be regarded as complete and permanent, the available evidence does not seem to warrant a positive conclusion, as the reported instances of cure of any considerable duration are still so few.

The general mortality of the operation of splenectomy performed for splenic anæmia cannot be stated with accuracy. Naturally the risk of the operation varies with the extent and duration of the disease and the special conditions found. Relatively early operation would of course show a lower mortality than late operation undertaken only as a last resort. In Armstrong's series the mortality was 28 per cent., but probably this figure is much too low, as fatal operations are not often reported. The mortality is caused chiefly by uncontrollable hemorrhage, either primary or secondary. Extensive adhesions firmly uniting the spleen to the diaphragm and surrounding structures are often found, and render successful removal a formidable and dangerous operation. It might seem wise to abandon the attempt if after exploratory laparotomy the actual conditions encountered rendered the removal of the spleen extra hazardous.

Preparatory to operation the patient's general condition should be raised to the highest point attainable by means of general, hygienic, and medicinal agents. Probably, also, the preliminary use of the *x*-rays over the spleen will be found to be of value in rendering subsequent splenectomy easier and safer by reason of the reduction in the size of the spleen and the restriction of its excessive vascular connections.

[1] *Annals of Surgery*, 1901, xxxiv, p. 111.
[2] *British Medical Journal*, November 10, 1906, p. 1273.
[3] *Zentralblatt f. Chir.*, 1906, Nr. 28, p. 112.

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KALA-AZAR. TROPICAL FEBRILE SPLENOMEGALY.[1]

Synonyms.—Kala-azar (black fever), tropical febrile splenomegaly, Assam fever (from Assam, India), dum-dum fever (from Dum-Dum, India), Burdwan fever (from Burdwan, India), kala dunkh or kala dukh, etc.

Definition.—A disease, endemic in certain tropical and subtropical countries in the Eastern Hemisphere and epidemic in parts of India, caused by a protozoal organism, the "Leishman-Donovan body," characterized by a chronic, irregular type of fever, marked splenomegaly, emaciation and cachexia, and terminating after several months or years in death from inanition or intercurrent infection or in gradual recovery in a small minority of cases.

Geographical Distribution.—The disease is widespread in India, limited apparently to its eastern side, except for occasional imported cases elsewhere. It occurs in sporadic, endemic, and epidemic form in that country, where it has its strongest hold. It is found both in the larger cities, Calcutta, Madras, etc., and especially in the country districts. In Assam, India, it is widely distributed and exists in its worst epidemic form. The spread of this epidemic up the Assam Valley has been very thoroughly studied by Leonard Rogers, whose valuable recent *Milroy Lectures on Kala-azar*[2] have been freely drawn upon in writing this article. Outside of India, the disease, confirmed by finding its parasite, has been reported from China, Egypt, Arabia, Tunis, Algiers, and elsewhere. Cases clinically similar have been reported from the Philippine Islands, but the parasite has been found wanting (Musgrave, Wherry, and Woolley). No cases have yet been reported from the Western Hemisphere, although it seems likely that the disease will be found existing in or introduced into any part of the tropics. Occasional cases have occurred in Europe in persons invalided from the tropics.

Historical.—The disease seems to have existed in India for centuries in its sporadic form and was mistaken for malarial cachexia until the discovery of its parasite, in 1903. About 1870 it broke out in Assam, India, in epidemic form and since then has continued its ravages, slowly creeping up the Assam Valley along the lines of communication for three hundred miles, wiping out whole families and villages and leaving depopulated districts and desolation in its wake. The British Government at different times sent out special commissioners to study the disease. These and other investigators reported the nature of the disease variously, as malarial cachexia, ankylostomiasis, Malta fever, dysentery, an independent disease of unknown nature, and various combinations of these several affections. No real advance was made until the discovery of the parasite by Leishman, reported in 1903.

Etiology.—Discovery of the Parasite.—The parasite now generally accepted as the causal agent of the disease, and commonly called the "Leishman body" or "Leishman-Donovan body," was first observed, November,

[1] The subject of Kala-azar, which properly belongs elsewhere, is placed in this section for several reasons, chiefly for convenience of reference, because the splenomegaly is the most important objective sign, and the causal agent has only recently been discovered.—EDITOR.

[2] *British Medical Journal*, February 23, March 2, and March 9, 1907.

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1900, by W. B. Leishman, at Netley, England, in Romanowsky-stained spleen smears made after necropsy on a soldier invalided for tropical splenomegaly from Dum-Dum, in Bengal, India. Leishman[1] did not publish his observations until May, 1903, and believed that the parasite found was a degenerate trypanosome. Donovan[2] at once, July, 1903, confirmed Leishman's discovery by finding similar bodies in the spleen of patients dying from prolonged fever in Madras and also in fresh blood obtained by spleen puncture from a living patient affected with tropical splenomegaly. Many other observers soon added their confirmation of these findings: Marchand (1903) at Leipsic, in the spleen, bone-marrow, and liver of a German soldier who had died from febrile splenomegaly acquired apparently in the recent Pekin campaign; Manson and Low (1904), in England, in a European invalided from India; Phillips (1904), in natives of Arabia and Egypt by spleen puncture; Bentley (1904), Rogers (1904), and others in Assam in numerous victims of kala-azar; Airde (1905) in Hankow, China, by spleen puncture in a case of splenomegaly; James (1905) in India in 67 out of 68 cases of kala-azar, etc.

"Wright's Bodies."—In the meantime, in December, 1903, J. H. Wright,[3] of Boston, published a description of bodies apparently identical with the Leishman bodies, found in the inflammatory tissue curetted from the base of an ulcer in a case of tropical sore ("Delhi sore") in an immigrant child from Armenia. Wright proposed for this parasite the name, *Helcosoma tropicum*. Wright's discovery of such parasites in tropical ulcer was confirmed by James (1904), Christophers (1904), and numerous subsequent observers. The relation of Wright's bodies to the apparently similar Leishman bodies of kala-azar will be discussed below, and for the present may be dismissed as apparent and not real.

Distribution of the Parasite in the Body.—The Leishman bodies in kala-azar were found most numerously in the spleen, liver, and bone-marrow, but also in the mesenteric glands, kidney, brain, intestinal ulcers, inflammatory effusions—in fact, in most of the organs. They have not been found in the urine or fæces. The parasites were found sometimes free but more commonly enclosed in swollen endothelial cells or macrophages or among cell detritus. Lately, Donovan, Christophers, James, Patton, and others have reported finding the Leishman bodies in leukocytes, generally the polynuclears, in the circulating blood. Donovan found them in the peripheral blood in 75 per cent., and Patton in an even larger percentage of selected advance cases of kala-azar in India.

Description of the Parasite.—The parasite, as found in the human body, requires staining by the Romanowsky stain or some modification for its recognition, and, thus stained, is seen as a small, sharply defined, generally round or oval, sometimes oat-shaped body, about the size of a blood platelet (2 to 4 μ in diameter), with faintly stained protoplasm and two characteristic chromatin masses which are clearly brought out by the stain as lilac-colored bodies, usually placed at the opposite sides of the lesser diameter of the parasite. The larger mass, the macronucleus, has a variable shape, generally round or oval, and is placed at one side of the parasite at its

[1] *British Medical Journal*, May 30, 1903, p. 1252.
[2] *Ibid.*, July 11, 1903, p. 79.
[3] *Journal of Medical Research*, December, 1903, vol. x, No. 3, p. 472.

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periphery. The much smaller micronucleus is generally rod-shaped or round, much more deeply stained than the macronucleus and placed near the other side of the parasite. The parasites in smears from the spleen or liver may be seen in enormous numbers contained in macrophages or lying in a matrix of cell detritus. In advanced cases the parasites may also be found within leukocytes in the peripheral blood. This is the Leishman body as found in the human body, no other forms or developmental stages having been discovered within the body. (See Plate IX.)

Cultivation of the Parasite.—In 1904, Leonard Rogers succeeded in cultivating the parasite outside the human body in infected blood, obtained by spleen puncture from kala-azar patients, to which was added normal salt solution and weak sodium citrate solution. He subsequently modified this medium by adding citric acid to the point of faint acidity. In this medium, kept free from bacterial contamination and at an optimum temperature of 20° to 22° C., the Leishman bodies rapidly multiplied and in three or four days passed through a series of developmental stages, briefly described as longitudinal division, enlargement and final evolution of flagellated, actively motile, elongated forms, which were arranged circularly in large rosettes with the single flagellum of each individual directed inwardly toward the centre of the group. The fully developed organism was a long, oat-shaped body, with the larger macronucleus near its centre, the small, rod-shaped micronucleus at one end surrounded by a round, clear, eosin-staining body, and a single flagellum springing apparently from this eosin body, but in reality from the micronucleus. The flagellum was long and slender and showed no trace of an undulating membrane. The parasite was grown between 15° and 25° C., best at about 22° C., and was quickly destroyed by accidental bacterial contamination. Rogers' important advance in the cultivation of the parasite was soon amply confirmed by many workers (Chatterjee, Christophers, Statham, Leishman, etc.).

Feeding Experiments.—*The Bedbug.*—Patton[1] (1906–07), in Madras, by feeding bedbugs on spleen blood from kala-azar patients, claims to have succeeded in producing the full development of the parasite in the bedbug's

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DESCRIPTION OF PLATE IX. (Rogers.)

(*Magnification of all the figures* 1500 *diameters.*)

I.—Undeveloped Leishman-Donovan bodies from spleen-puncture film.
II.—Early stages of development, from two days' culture in acidified citrated blood: 1 and 2, body and macronucleus enlarged; 3 and 4, first appearance of eosin body; 5 and 6, elongation and subdivision; 7 and 8, first appearance of flagellum.
III.—Stages of division of the early flagellated forms.
IV.—Double, long, swimming forms.
V.—Fully developed, long, free, active single cells.
VI.—Degenerate forms.
VII.—Undeveloped forms in a white corpuscle.
VIII.—Early stages of development in a degenerating white corpuscle.
IX.—Stage in the formation of rosette.
X.—Separated flagella with micronuclei attached.
XI.—Rosette breaking up into free forms.
XII.—Small complete rosette.

[1] Reported by Rogers, *British Medical Journal*, March 9, 1907, p. 561.

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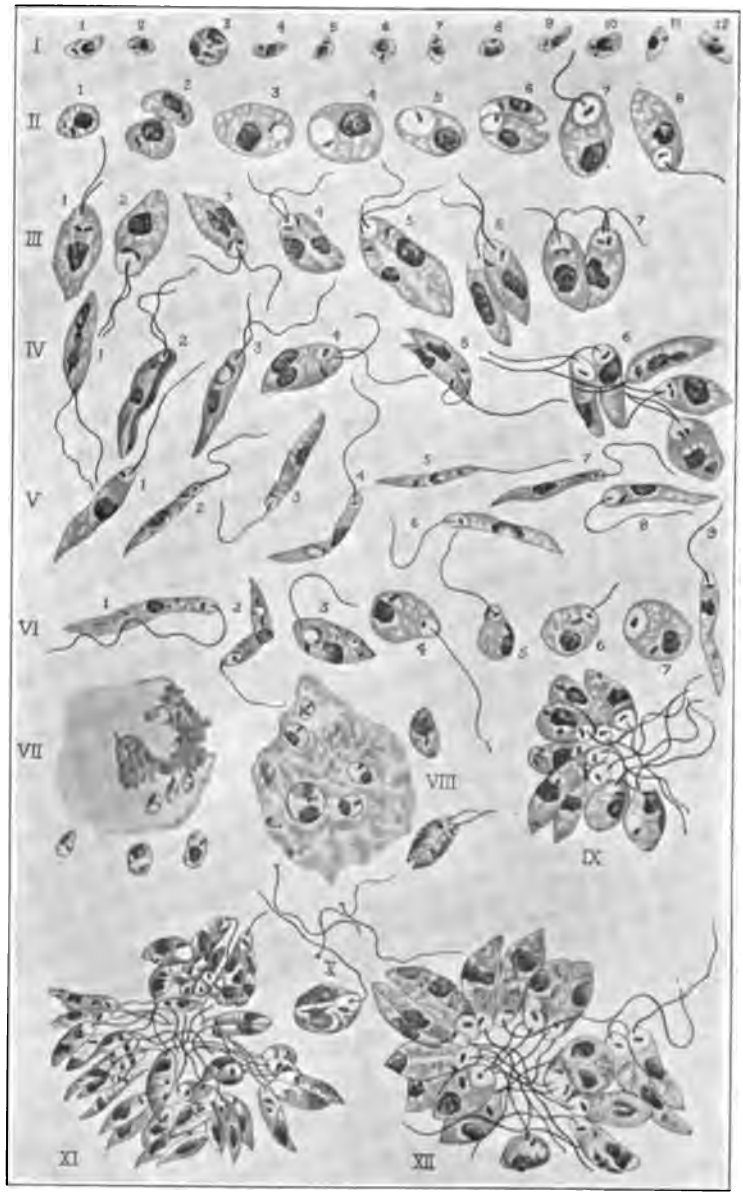
PLATE IX



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stomach cavity, as already obtained by Rogers in artificial blood medium. Similar experiments with mosquitoes, ticks, and lice were negative. The common house flea was not investigated. Patton's success with bedbugs proved complete only when he conducted his experiments in the cooler winter months with a temperature which Rogers had found necessary to the successful cultivation of the parasite. Patton, in a recent letter to Rogers, is quoted by the latter as follows: "I have got the complete cycle of the parasite up to completely developed flagellates. . . . There is no shadow of a doubt that the bedbug transmits the disease." Patton,[1] in his report of his experiments published in 1907, adds a postscript to his paper, stating, "Since writing the above I have found in the bedbug (*Cimex macrocephalus* Fieber) all the intermediate stages of development and numerous fully developed flagellates similar to those seen in cultures of splenic blood." Patton's work has not yet been reported confirmed. It may be added that Rogers had previously suspected the bedbug as the carrier of the disease.

The bedbug incriminated by Patton is not the common bedbug *Cimex lectularius*, Linnaeus, but another species, *Cimex rotundatus*, Signoret (*Cimex macrocephalus*, Fieber). The latter species has been found by Patton distributed throughout India, Burma, Assam, Malay, Aden, Mauritius, Réunion, Sierra Leone, and in the Western Hemisphere, in Porto Rico and St. Vincent.

In this connection, it may be remarked that the few attempts that have been reported to inoculate kala-azar into animals have all failed. Mackie (1907) injected material rich in parasites under the skin, into the peritoneal cavity, spleen, liver, vein, stomach, and rectum in monkeys, goats, rabbits, rats, guinea-pigs, and pigeons, with entirely negative results in all cases.

Nature of the Parasites.—Various views have been expressed as to the biological position of the newly discovered parasite. Leishman believed that it represented a degenerated form of trypanosome; Laveran and Mesnil regarded it as a piroplasma and proposed the name *Piroplasma donovani;* Christophers thought it a spore stage of a microsporidium; Ross believed that it represented a new genus and proposed the name *Leishmania donovani*, for its discoverers; Rogers concluded that the organism belonged to the order *Herpetomonas* and proposed the name *Herpetomonas of Kala-azar;* Schaudinn, Hartmann, and other authorities on protozoa regarded it as a flagellate differing from any previously known form, of uncertain biological position, and, therefore, appropriately called *Leishmania donovani*, as a non-committal designation, suggested by Ross. The last view is the one at present most acceptable until the working out of the further life-cycle of the organism makes plain its true nature.

Contributing Factors in Etiology.—*Climate.*—The disease is found only in warm countries, except for occasional imported cases. Rogers thinks that the evidence goes to make it highly probable that infection and the onset of the disease occur chiefly during the cooler months of the year in India, *i. e.*, November to April, although the frequently long incubation period may delay the onset of symtoms to any period of the year. Tending to support this view are the facts that Rogers succeeded in cultivating the organism only

[1] *Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India*, Calcutta, 1907, No. 27, new series.

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at a range of temperature, 60° F. to 75° F., which is commonly found in India during the cold season, and that Patton's feeding experiments with bedbugs in Madras were fully successful only at this period of the year. In extending up the Assam Valley, the disease was always checked as it approached the high elevations, where the weather was too cold. There is no indication of relation to moisture or rainfall.

Sex and Age.—There is no difference in the sex incidence. Cases in husband and wife are common. Childhood is the age of predilection and thereafter each succeeding decade of life shows a steadily decreasing incidence; 20 to 40 per cent. of all cases occur under the age of ten years, 50 to 70 per-cent. under the age of twenty years; after forty years the disease is relatively infrequent.

Race.—In India the disease is largely confined to the natives, although sporadic cases in Europeans in Calcutta and other cities are not very uncommon. According to Rogers, of 87 such cases in Europeans over 87 per cent. were born and bred in India and only about 13 per cent. were immigrants from Europe. Foreigners attacked belong almost invariably to the lower classes and live in the native quarters, although of course exceptions occur.

Transmission.—All the evidence points clearly to the transmission of the disease by intimate personal contact with infected persons and especially by sleeping in infected houses, which account for the vast majority of cases. Europeans have been known to acquire the disease by cohabiting with infected native women even, in certain instances, when the native women have visited the quarters of the Europeans. A single night of such cohabitation has been followed by infection in the exposed foreigner (Rogers).

This would prove that the active agent of infection can be carried on the person or clothing of those harboring the disease. Casual relations with such people seem to be practically free of danger, although, perhaps, not entirely so, if, as now seems possible, the bedbug is proved to be the inoculator of the parasite. The slow progress of the disease from house to house and along the lines of communication can, in almost all instances, be traced to direct transmission from infected persons.

Pathology.—The *skin* is muddy and often shows varying degrees of diffuse or irregular pigmentation which may extend to the mucous membrane of the mouth. Moderate icterus may be found in some cases, generally associated with cirrhosis of the liver.

The *spleen* is invariably greatly enlarged, pigmented, firm, and friable, but not sclerotic, as a rule. Its substance is crowded with innumerable Leishman bodies filling the interior of the swollen cells and scattered loose in the lymph and blood spaces mingled with cell detritus. Infarcts of the spleen occur occasionally and perisplenitis with adhesions is common.

The *liver* is enlarged, often enormous, firm and friable, pigmented, and contains an excess of iron. The parasites may be present in enormous number, contained apparently in the swollen endothelial cells of the capillaries and lymph channels or lying among the detritus of such degenerated cells. The parenchyma cells of the liver, although often extensively degenerated, are not invaded by the parasite. The centres of the lobules are marked with a whitish deposit, consisting of masses of parasites enclosed in endothelial cells or scattered among the cell detritus. Cirrhosis of the liver is common, usually intralobular, sometimes, also, of the perilobular or portal type.

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The *bone-marrow* is loaded with parasites contained in macrophages and, also, scantily in leukocytes and myelocytes.

Otherwise, the morbid anatomy is that common to all diseases associated with wasting, anæmia, and cachexia, namely, fatty degeneration of the organs, œdema, effusions in the serous cavities, hemorrhages, etc. The pathology of the disease is further amplified by that of various complications, which, in the majority of cases, are the direct cause of death, especially dysentery, cancrum oris, pneumonia, meningitis, pericarditis, septicæmia, etc.

Clinical Picture, Symptoms, and Course.—The disease commences with high fever, often preceded by a rigor or chill, and sometimes by vomiting and headache. The fever of onset varies in type, being most commonly remittent or sub-continued, less frequently intermittent. According to Rogers, the early remittent fever is often specially characterized by a daily double or sometimes triple rise for several days without treatment. These variations in the daily temperature of the early fever are thought to be of importance in helping to differentiate kala-azar from typhoid fever, with which it is likely to be confused in sporadic cases. The pulse is accelerated somewhat more than in typhoid fever. In other cases the fever of onset is of a low, continued type, with slight daily variations, or it may be intermittent. The original fever lasts usually two to six weeks or longer, during which the spleen enlarges rapidly and, perhaps, also, the liver to a slight extent. A period of apyrexia follows the original fever, accompanied by improvement in the patient's condition, which in turn is succeeded by a second period of fever, and thus periods of pyrexia and apyrexia of varying length alternate as the disease progresses. The secondary accessions of fever show marked variation in type, remittent and intermittent forms often alternating over long periods, with spells of apyrexia interspersed, until finally in many cases a low type of intermittent or continued fever develops and persists for months.

During the periods of pyrexia, especially the remittent fever, the patient rapidly grows anæmic, wastes, and has great enlargement of the spleen and moderate enlargement of the liver, with tenderness over these organs. With the enlargement of the spleen and liver and the emaciation and cachexia, the patient presents a striking picture of a pot-bellied skeleton.

Among the common minor symptoms may be mentioned delirium, severe headache, usually frontal, neuritic pains, pains and swelling over the joints, slight œdema of the extremities, vomiting, diarrhœa, wasting and loss of the hair, petechial eruptions, epistaxis, hemorrhages from the gums, etc. Dysenteric symptoms—bloody, mucous stools—occur especially frequently, and are almost the rule in advanced cases.

Cutaneous Symptoms.—In advanced cases the skin is sallow or earthy, often with a moderate, diffuse or patchy, grayish pigmentation, which may also involve the buccal mucous membrane. The darkness of the skin (kala-azar; black fever) is not usually extreme, often slight. The expression of the face is heavy and lethargic. Icterus, secondary to cirrhosis of the liver, is not uncommon late in the disease. Petechiæ in the skin are frequent. Œdema of the extremities may occur with anæmia or associated with cirrhosis of the liver. Night-sweats, following the common afternoon exacerbations of temperature, may be a marked feature. Pains and swellings near the joints, occurring early in the disease, with fever and sweats, often lead to a diagnosis of rheumatism.

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Spleen.—The spleen is invariably enlarged, being appreciable in the early stage of the fever as a soft spleen tumor and rapidly increasing in size and firmness during the subsequent febrile attacks. The spleen reaches the navel in 60 to 80 per cent. of cases and the anterior superior spine of the ilium in from 10 to 20 per cent. It is rarely found less than a hand's breadth below the costal margin. During the periods of apyrexia and especially during the prolonged post-febrile period, often occurring late in the course of the disease, the spleen tumor may undergo marked reduction. Dragging pains over the enlarged organ are complained of or pain of a more severe character in case of infarct or perisplenitis.

Liver.—The liver usually enlarges with the spleen, but later and to a less degree. After several months it may occasionally reach the navel and in rare cases is even larger than the spleen. Symptoms of cirrhosis with portal and biliary obstruction, *i. e.*, icterus, ascites, gastro-enteric disturbances, etc., are not infrequent late in the disease. Perihepatitis with adhesions may lead to tenderness and pain.

Blood.—This shows a secondary type of anæmia which seldom reaches an extreme grade except from complications. Loss of red corpuscles to 2,500,000 per cmm. and of hæmoglobin to 35 to 40 per cent. in advanced cases is the rule. Occasional normoblasts occur. Poikilocytosis and polychromatophilia are unusual except in the last stage. The leukocytes are never increased in uncomplicated cases. A pronounced leukopænia is the rule, not infrequently to 1000 or less per cmm. This is further characterized by a constant and marked relative increase of the lymphocytes and large mononuclears with a corresponding reduction in the polymorphonuclear neutrophiles. The eosinophiles may be considerably increased in certain cases, probably due to concurrent ankylostomiasis and other causes. As already stated, the Leishman bodies may be found within the leukocytes, usually the polynuclears, in advanced cases. The platelets are increased in number.

Urine.—The urine may show traces of albumin, perhaps occasional casts, a deposit of phosphates, and sometimes it is high-colored from red corpuscles. Parasites are not found in the urine.

Duration.—The duration of the disease, on the average, is from six to nine months, but may cover a period of two or three or more years, ending in the great majority of cases in death, which may occur at any period of the disease with exacerbation of fever, but usually results from inanition complicated with some terminal infection.

Complications.—As seen in India, kala-azar is frequently complicated by such common diseases as malaria, ankylostomiasis, dysentery, etc., and is usually brought to its fatal termination by some inflammatory complication. In 40 autopsies made by Rogers, all but 7 showed complicating infections or local conditions contributing toward death, as follows: pneumonia, 11; dysentery, 10; cancrum oris, 7; pneumococcus meningitis, 2; purpura, 2; cerebral hemorrhage, 2; pulmonary tuberculosis, 2; pericarditis, 1.

Diagnosis.—The disease occurs in India in sporadic, endemic, and epidemic form. The sporadic cases are the ones most liable to be encountered by physicians in the tropics and are the cases that are most likely to go to the autopsy-room for diagnosis. The diagnosis is made certain only by finding the parasites, for which purpose thorough and repeated blood examinations should be made in view of Donovan's and Patton's success in finding

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the parasites in the blood in about 75 per cent. of advanced cases. If blood examination prove negative, spleen or liver puncture may be resorted to in selected cases and will prove positive for the parasites in practically all cases at all stages of the disease. A rather small needle should be used and need not be introduced deeply into the organ. The few drops of contents should be spread on several coverslips, stained by some form of the Romanowsky stain, and examined with an oil-immersion lens. In view of the not infrequent fatal hemorrhage following spleen puncture, this procedure should not be too lightly undertaken. Special contra-indications to its employment are marked anæmia, asthenia, and a hemorrhagic tendency, with increased coagulation time of the blood. Calcium chloride or lactate should be administered before and after the puncture, to increase the coagulability of the blood and reduce the danger of hemorrhage. It is advisable also to reduce the movements of the spleen in abdominal respirations by adjusting a tight abdominal bandage during and after the operation and keeping the patient at rest in bed until all danger is past. Puncture of the liver may be resorted to successfully and with less danger of fatal hemorrhage.

In the absence of spleen or liver puncture or successful blood examination, the diagnosis must be suggested by tropical residence and the general features of the disease, *i. e.*, marked splenomegaly, enlargement of the liver, progressive emaciation, cachexia, discolored skin, irregular fever, etc., and by exclusion of other etiological factors. Sporadic cases, seen during the first period of fever, offer great difficulty and are particularly appropriate for spleen puncture, as early diagnosis would give the patient the benefit of suitable treatment and the best chance for recovery.

Differential Diagnosis.—The diseases most commonly confused with kala-azar are typhoid fever, malarial fever, Malta fever, rheumatic fever, ankylostomiasis, leukæmia, splenic anæmia, and other forms of splenomegaly. The malarial fevers are excluded by the continued absence of malarial parasites in the blood and by the quinine test; ankylostomiasis by negative examinations of the stools for the ankylostoma and by thymol treatment; leukæmia by the absence of its well-known blood picture; rheumatic fever by the marked splenic enlargement, salicylic treatment, etc.; splenic anæmia by the irregular fever and general considerations; typhoid fever by the absence of the Widal reaction and the subsequent course of the disease; Malta fever by the absence of the specific, agglutinative serum reaction with cultures of *Micrococcus militensis*, used in sufficient dilution, etc.

The constant presence in the granulation tissue of tropical ulcer of parasites, Wright's bodies, morphologically indistinguishable from the Leishman bodies of kala-azar, might seem to indicate that kala-azar and tropical ulcer were different forms of an identical infection. It would be premature, however, to draw such a conclusion from our present meagre knowledge, and, indeed, it would seem more probable that diseases so clearly unlike in every other respect would be found to be wholly distinct and that Leishman bodies and Wright's bodies were, in fact, different species.

Prognosis.—This is briefly summarized by the mortality figures, 96 to 98 per cent. Thorough quinine treatment is claimed by Rogers to reduce the mortality to about 75 per cent.

Treatment.—Prophylaxis.—With the parasite known and the bed-bug incriminated as its possible inoculator, as well as from the numerous observations by Bentley, Price, Rogers, and others on the successful control

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of the disease by measures directed against house infection, the indications for prevention seem clear. Until the relation of the bedbug to the disease is cleared up, this pest should be exterminated in infected houses by appropriate measures, such as sulphur fumigation, sterilizing the bedding, clothing, and interiors of dwellings, or, better still, by burning such houses and their contents. Rigid quarantine against infected individuals, houses, and localities should be enforced. Foreigners in endemic centres should be warned of the danger of association with the natives. The disease seems to be communicated only by the most intimate contact with infected persons or dwellings, especially by sleeping with such persons or in their houses. Casual relations with infected natives seem almost free from danger, although its possibility should never be neglected.

Treatment by Drugs.—The terrible mortality tells its own mournful story of therapeutic impotence. Quinine, alone, has been found of value, although by many of the most experienced physicians, who have had unusual opportunity for studying its effects in India, it has been discarded as worthless. Rogers is conspicuous by his insistence on the efficacy of this drug. He uses it in large doses, gradually increased to 60 and sometimes to 90 grains per day, and continued in these large doses for weeks and, if necessary, for months. He claims that the high remittent fever is reduced and slowly assumes a low, continued, benign form which in favorable cases gradually exhausts itself and is followed by apyrexia and improvement. After the apyrexia has lasted several months, complete recovery is the rule and relapses are exceptional. As soon as the temperature has fallen to the low continued or intermittent type under the use of such large doses of quinine, Rogers reduces the dose to about 20 grains daily, which is sufficient to keep the temperature from returning to its previous level. This method of treatment was systematically employed by Price in 500 consecutive cases with permanent recovery in 25 per cent., contrasted with recovery in only 4 per cent. of several hundred cases previously treated by the same physician in which the quinine treatment was not so vigorously and systematically used. In view of these results and the admitted failure of all other methods of treatment, it seems fair that Rogers' method of quinine treatment should be given the benefit of any doubt.

Needless to add, tonics, such as iron and arsenic, and careful attention to the patient's general care should be suitably employed. Complications must be treated as they arise. Malaria and ankylostomiasis, which are common complications in India, can be suppressed, respectively, by quinine and thymol. Improvement and even complete recovery in rare cases have been observed to follow various intercurrent septic infections.

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CHAPTER XVIII.

DISEASES OF THE THYMUS.

By ALDRED SCOTT WARTHIN, Ph.D., M.D.

General Considerations.—The thymus gland is originally an epithelial structure, arising as paired tubular epithelial diverticula from the dorsal portion of the pharyngeal aspect of the third visceral clefts. The two lobes of the gland are formed by the extension of these diverticula downward along the sides of the trachea toward the pericardium, expanding below to meet each other. The communication with the pharyngeal clefts is ultimately lost, while solid epithelial branches bud out from the expanded lower portion in a manner suggestive of a branched tubular gland. At the same time there is a subepithelial formation of lymphoid tissue which extends between and invades the epithelial portions of the organ until it finally becomes the most prominent histological feature. The epithelial elements become atrophic and undergo various retrograde changes, but their remnants persist in the form of the concentric corpuscles of Hassall, in some cases at least, if not in all, to the end of adult life. At birth the lymphoid character of the organ is so marked that it is usually classed with the lymph glands. It consists of a pinkish mass lying in the upper portion of the anterior mediastinum behind the manubrium, the two lateral lobes appearing more or less fused together, although often separated by a fissure. Diverging prolongations usually extend downward over the base of the pericardium, and less frequently similar ones extend upward toward the thyroid. The microscopic features of the gland are an investing fibrous capsule, connective-tissue trabeculæ, cortex of lymphoid tissue, and a medullary portion containing the Hassall's corpuscles and many eosinophile cells. Within apparently normal limits the weight of the thymus appears to vary greatly, and authorities differ widely in the standard of weight given. There can be but little doubt that the commonly accepted weights are too high. In common with Dudgeon, the writer believes that from birth up to the age of two years the average weight of the thymus is about seven to ten grams, and that glands, therefore, weighing twenty to thirty grams must be regarded as enlarged. The fullest development of the organ is reached at the end of two years. Atrophy of the lymphoid tissue, with its replacement by adipose and fibrous connective tissues, takes place gradually from the second year to the advent of puberty, and more rapidly after this time, so that in adults the thymus comes to be represented by a mass of fibrous tissue and fat containing small nodes of lymphoid tissue in which Hassall's corpuscles persist, even to extreme old age. A careful microscopic examination of the thymic fat of adults will show the presence of some thymic tissue, so that the commonly accepted statements that the thymus is entirely absent in adults must be revised.

The anatomical status of the thymus cannot be said to be definitely fixed

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at the present time. Some writers would class it with the ductless glands; others place it without question among the lymphoid organs. Basch may be taken as representing an extreme of the first view. He holds that the thymus is different from the lymph glands in all respects, embryologically, histologically, and chemically. He believes the "supposed" lymphocytes of the organ to be of epithelial origin and to retain their epithelial character. The opposite view is held, however, by an increasing number of writers. Maximow may be taken as a representative of this class. He holds that the lymphoid tissue of the thymus is truly lymphoid, and that it arises from histogenetic wandering cells developing in the mesenchyme from the endothelium and perithelium of the bloodvessels at a time when the thymus lobes show a pure epithelial character. The lymphoid cells wander in between the epithelium and change into typical large lymphocytes, increasing in number until the epithelial elements are thrown into the background. Finally, the organ comes to consist chiefly of masses of typical small lymphocytes, some erythroblasts, and myelocytes. The epithelium of the organ serves only as a favorable place for the development of the lymphoid tissue, as in the case of the tonsils. Indeed, the thymus may be regarded as a homologue of the latter. While we cannot at the present time absolutely deny a place to the thymus among the glands producing an internal secretion, the mass of evidence in favor of such a function is, when weighed without prejudice, very small indeed. And until the question is settled the best course to pursue seems to be to class the thymus with the lymphoid organs, inasmuch as the knowledge we do possess concerning its development and structure favors this view.

Of the *function* of the thymus we have as yet no definite knowledge. It has been assumed to be that of lymphoid tissue in general, and there can be no doubt that lymphocytes and eosinophile cells are formed in its lymphoid tissue. An erythropoietic function has not been shown to occur under normal conditions. We are wholly ignorant of the significance and function of the epithelial portion of the organ. Various writers have asserted that the thymus possesses certain vegetative functions, particularly in connection with the development of the bones, central nervous system, sexual apparatus, and the general metabolism of the body. With such hypotheses as a basis, numerous attempts have been made to establish the position of the thymus as an organ producing an internal secretion, and functional relationships have been assumed between it and the hypophysis, sexual glands, and the chromaffinic tissues. Whatever this hypothetical function may be, the majority of writers concede it to be only a temporary function in a certain phase of development of the body. Baumann demonstrated the presence of iodine in thymic tissue, and the investigations of Weintraud and Mayer have shown that thymus feeding causes a striking increase in the output of uric acid. Such an increase does not occur after thyroid feeding. Thymectomy experiments in animals have given contradictory results, but according to Thiroloix and Bernard, and Abelous and Billard, the removal of the thymus in rabbits and frogs gives rise to symptoms of intoxication proving fatal within a few weeks. When but half of the organ is removed death of the animal does not occur, but the remaining half of the gland becomes hypertrophic. Grimani and others deny that the removal of the thymus causes death in rabbits. Paton and Goodall were unable to make out any rachitogenic effects following extirpation, but Basch claims that the removal of the

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thymus in dogs causes an increased excretion of lime-salts and a deficient ossification ("experimental rachitis"). Complete thymectomy in children has apparently no effect upon the blood or nutrition, but König saw a florid rachitis develop in an infant whose thymus was removed when nine weeks old. An inter-relationship between the functions of the thymus and spleen has also been assumed by some writers, but according to Paton and Goodall the simultaneous removal of thymus and spleen in guinea-pigs is without effect upon the nutrition, growth, development, and blood-formation of the animal. Injections of extracts of the thymus cause lowering of blood pressure, cardiac weakness, dyspnœa, and finally death. Since similar effects may be produced by extracts of practically all other tissues, it is probable that the function of the thymus is not concerned with any direct action upon the vasomotor system.

Experimental work by Paton and Henderson apparently shows that there is a reciprocal action between the thymus and testes, each checking the growth of the other. Castration delays involution of the thymus, while removal of the thymus causes a more rapid development of the testes. Experiments in thymus grafting have, as a rule, been negative. According to Grimani the transplantation of the thymus does not lower the hæmoglobin content of the blood, but is followed by a leukocytosis. The general nutrition suffers, but improvement follows the injection of thymus extract.

From the surface of the fresh thymus a thick fluid may be expressed. It is normally sterile, possesses an acid reaction, and consists chiefly of lymphocytes, with occasional eosinophiles, large hyaline cells, and polymorphonuclear leukocytes. This fluid has been regarded by some writers as representing the normal secretion of the gland, by others it has been interpreted as signifying various pathological changes. It is probably for the greater part the result of a postmortem change or digestion, as the fluid increases in amount in proportion to the time elapsing between death and autopsy. Ultimately the entire central portion of the thymic lobes may become liquefied. Inasmuch as such a postmortem softening or digestion does not occur in the lymphoid tissue in other parts of the body, it may be assumed that there is some substance within the thymus responsible for this liquefaction (proteolytic enzymes).

According to the literature, the diseases of the thymus are rare. The pathology of this organ has been strangely neglected during the past two decades, and with the exception of two conditions, atrophy and hypertrophy, but little has been added to our knowledge concerning its morbid states. The few studies that have been made within recent years have, however, served to clear up some of the common misinterpretations of certain histological peculiarities of this interesting organ.

ANOMALIES OF THE THYMUS.

Total absence of the thymus has been reported in a number of cases, and an attempt has been made to show some relationship between this anomaly and hæmophilia, general disturbances of development, infantilism, etc. Inasmuch as these observations were based upon the gross appearances alone, they cannot be accepted as wholly conclusive. A microscopic examination of the entire mass of fat and fibrous tissue would have to be carried out

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in order to establish the diagnosis of a complete absence of thymic tissue. In the case of true acephalic monsters the thymus may be entirely absent, and up to the present time such cases are the only ones in which a total absence of the organ has been definitely shown to exist. In acephalic, anencephalic, and hemicephalic monsters with developed thoracic cavities, the thymus may be smaller than normal or may be hyperplastic. In such cases the adrenals may be wholly absent or very small, and the hyperplasia of the thymus has been regarded as compensatory for the chromaffinic tissues.

Accessory thymic nodules may be found in the thyroid region and in the periphery of the thymic area, and may present as subcutaneous tumors in the neck. They are to be regarded as persistent areas cut off from the main organ through the atrophy or non-development of the intervening portion. On microscopic examination, proof of their continuity with the main body of the thymus can often be found. Our pathological knowledge of accessory thymic tissue is practically nothing, but it is probable that some of the deep-seated primary cervical carcinomata of unknown origin may arise from such accessory thymic nodules. At least one case has been reported of an aberrant thymus undergoing hyperplasia and requiring surgical removal.

The cervical lobes of the thymus rarely extend to the level of the thyroid, but occasionally they may reach higher, even to the floor of the mouth. A third intermediate lobe is occasionally seen, sometimes extending downward toward the heart, in other cases, upward into the neck. The main lobes of the organ, both upper and lower, are often very tortuous and nodular, sometimes consisting of masses of thymic tissues strung together by narrow connecting cords or bands. Persistence of the original tubular structure of portions of the organ is not uncommon, giving rise to the appearance of gland tubules.

CIRCULATORY DISTURBANCES OF THE THYMUS.

Congestion.—The bloodvessels are involved in the case of any general circulatory disturbance, such as anæmia or hyperæmia. The thymic veins may become greatly distended in chronic passive hyperæmia, particularly when due to cardiac lesions. As a result the thymus or the thymic fat may become much enlarged and reddened. Such a congestive enlargement of the tissues of the thymic area may be mistaken at autopsy for a hyperplastic or persistent thymus, but it will usually be found during the progress of the autopsy that the enlargement disappears and the tissues become paler. It is also probable that the most severe thymic congestion may disappear at death and leave no trace at autopsy. Marked venous hyperæmia of the thymus may be seen also in cases of asphyxia neonatorum, suffocation, pneumonia, diphtheria, etc., and possibly as the result of trauma. A careful differential diagnosis should be made in such cases from the hyperplastic thymus of the lymphatic constitution. As Dudgeon and others have pointed out, many cases diagnosed as "thymus death" are most probably due to "overlaying," but the coincident congestion of the thymus may have hastened suffocation. It must also be borne in mind that in the case of a hyperplastic thymus the acute increase in size due to an acute hyperæmia has been regarded by a number of writers as the direct cause of thymic stridor and sudden death, the increase in size being considered sufficient to bring about

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a fatal result through pressure upon the trachea, neighboring vessels, and nerves. From recently reported cases there can be no doubt that congestion of the thymus alone, even when the gland is of normal dimensions or under these, may cause asthma or sudden death through pressure upon the structures lying beneath it. At autopsy the congestion may have entirely disappeared, and the gland present dimensions usually regarded as normal. An added clinical interest has been given to congestion of the thymus by its occurrence after goitre operations. Since thymic hyperplasia is frequently associated with goitre, both the simple and exophthalmic forms, such a postoperative congestion of the enlarged thymus may result fatally. Gluck has reported death following thyroid operations with symptoms of cyanosis, dyspnœa, and pulmonary œdema. Dwornitschenko explains these cases as the result of an arterial congestion of the thymus. After the ligation of the thyroid branches of the thyroid artery this vessel sends its blood into the Rami thymici, causing an arterial congestion. The enlarged organ presses upon the vena anonyma and there is thus produced a secondary venous congestion.

Marked œdema of the thymus may be seen in cases of universal œdema, and may cause pressure symptoms. It is also possible that acute œdema of the gland may occur, cause pressure symptoms, and entirely disappear at death. When large saline injections are given in the pectoral region just before death the tissues of the thymus area and the anterior mediastinum may be found at autopsy to be markedly œdematous, and no pathological significance should be attached to such findings. Eosinophile cells are said to be absent in the thymus of cases of congenital heart lesions.

Hemorrhage.—The occurrence of small punctate hemorrhages in the thymus has been many times observed in newborn infants dying as the result of difficult labor, also in association with whooping-cough, empyema, bronchopneumonia, lobar pneumonia, asphyxia, suffocation, convulsions, hæmophilia, purpura hæmorrhagica, sepsis, status lymphaticus, epilepsy, phosphorus poisoning, etc. Dudgeon found hemorrhages in the substance of the thymus in about 95 per cent. of deaths from bronchopneumonia and lobar pneumonia. The small size of the extravasation deprives the condition of any clinical significance. Friedleben alone has observed a larger "apoplexy" of the thymus occurring in the case of sudden death in a marasmic infant suffering from diarrhœa. The clinical and pathological significance of such a case it is at present impossible to determine.

RETROGRADE CHANGES.

The normal retrograde changes must be carefully distinguished from those representing pathological changes. After the second year the lymphoid areas become reduced in size and there is an invasion of the gland by fat and fibrous connective tissue. The cells of the lymphoid areas retain their lymphocyte character, although greatly diminished in numbers, while the reticulum is increased. Fatty degeneration of both lymphoid cells and corpuscles of Hassall is found in the majority of thymus glands without reference to the general condition of the individual. It may be confined to the periphery of the lobules or may be general. It occurs so constantly that it must be regarded as a normal process. In the case of pathological atrophy

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the lymphoid cells are replaced more or less completely by cells of the type of fibroblasts or endothelial cells. Calcification, cystic softening, etc., of the corpuscles of Hassall are also to be classed with the retrograde changes occurring normally. It may be noted in this connection that after the second year the weight of the thymus cannot be taken as a criterion of its condition, since an atrophic thymus may weigh as much as a normal one, owing to the great amount of fibrous tissue present.

ATROPHY OF THE THYMUS.

Pathological atrophy of the thymus must be regarded as one of the essential morbid conditions of this organ. Since we are as yet wholly ignorant of the nature and significance of these abnormal forms of thymic atrophy, we may, for the present, at least, follow Dudgeon in classing them as primary or secondary according to the absence or presence of other pathological conditions explaining the atrophy.

Primary Atrophy.—The association of thymic atrophy with a progressive and fatal marasmus in children has been pointed out by a number of observers (Ruhräh, Dudgeon, etc.). In many cases no definite cause for the marasmus can be ascertained. Improper feeding, imperfect assimilation of food, congenital syphilis, toxæmia of unknown source, etc., are among the etiological factors given. The autopsy picture in these marasmic children is very striking. In addition to the marked wasting of the body or changes due to some terminal infection, the thymus is so reduced in size that it may easily be regarded as entirely absent. In the thymic area only a small mass of what appears to be œdematous connective tissue is found, which cuts with great resistance. The thick fluid seen normally is absent, and the lobular arrangement of the organ is not apparent. The weight of the entire thymic mass is usually about 2 grams. A fibrosis of more or less marked degree is present, the increase of connective tissue being diffuse and not limited to the interlobular portions of the gland. Fat cells may be either absent or present in the connective tissue. The arteries and veins may both show thickening of their walls. The cortex and medulla are not easily differentiated. The most striking histological change is the disappearance of the lymphoid cells and their replacement by cells of fibroblastic and endothelial type. Numerous giant cells resembling those found in the lymph glands in Hodgkin's disease may be present. The eosinophiles are apparently diminished. The corpuscles of Hassall are relatively increased; they show the ordinary retrograde changes. In the case of terminal infection, hemorrhages may be present in the thymic substance. In addition to this pathological picture, which agrees with the description given by Dudgeon, the writer would call attention to similar changes occurring in the spleen and lymph glands suggesting a general lymphoid exhaustion.

Secondary Atrophy.—Similar atrophic changes may be found in the thymus in cases of marked marasmus due to chronic tuberculosis, empyema, bronchiectasis, etc. Not all cases of secondary marasmus, however, are associated with marked thymic changes, while in primary marasmus the thymic atrophy appears to be constant. In the case of secondary atrophy the condition of the thymus might easily be explained as due to the existing chronic toxæmia or malnutrition. In general it may be said that thymic

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atrophy is coincident with wasting of the tissues in children, and that the state of nutrition of a child may be judged by the condition of this organ. In the thymic atrophy due to starvation there is no fibrosis, but the weight of the gland is much reduced.

In so far as the clinical significance of atrophy is concerned, but little can be said at the present time. It is very doubtful if the so-called primary form is anything more than a local expression of some condition, intoxication or malnutrition, in which there is a general lymphoid exhaustion. There is no reason at present to believe that the thymic atrophy has any causal relation to the marasmus. Nevertheless, it might be worth while to try thymus feeding or the use of thymic extract in cases of obscure infantile marasmus. Until the etiological factor is discovered and the true relationship between the marasmus and the condition of the thymus is known therapeutic attempts must be made wholly in the dark.

There are no thoroughly satisfactory observations of the occurrence of *amyloid* in the thymus. *Hyalin* of the type of that found in connective tissue has been described as occurring in the corpuscles of Hassall, but such statements rest upon faulty staining technique. The hyaline change seen normally in the corpuscles is of the nature of cornification or epithelial hyalin. *Calcification* of the corpuscles is to be regarded as a normal event, and is not to be misinterpreted. It follows the hyaline change in the corpuscles. *Cystic softening* of the corpuscles is to be similarly regarded. Pathological *pigmentation* of the thymus has also been recorded, but it is very probable that the mediastinal lymph glands were the tissues involved.

ENLARGEMENT OF THE THYMUS.

Synonyms.—Persistence of the thymus, hyperplasia, hypertrophy, congestion, status lymphaticus, etc.

General Considerations.—Enlargement was the earliest recorded pathological condition of this gland, and is the one most frequently observed at the present time. In practical importance it overshadows all the other morbid states of this organ. Its relation to congenital and infantile stridor, asthma, and sudden death, either with or without a coincident enlargement of the lymph glands, has given to thymic enlargement a clinical interest not shared in by the other affections of this gland.

While it was early recognized that enlargement of the thymus might be the direct etiological factor in the conditions mentioned above, it was due largely to the dictum of Friedleben (1858) that the acceptance of this point was delayed for half a century and a controversy aroused over it that still wages to some extent. Numerous arguments have been advanced for and against the view that an enlarged thymus may cause stridor, asthma, or sudden death through pressure upon the trachea and the other important structures lying beneath the organ. Inasmuch as in the older cases the thymic condition was discovered only at autopsy, it has hitherto been impossible to formulate a scheme for differential diagnosis during life. In recent years an increasing number of such cases has been studied before death, and the possibility of an antemortem diagnosis, as well as of therapeutic measures, has been demonstrated beyond any doubt. At the present time we can, therefore, make definite statements concerning both the pathology and the clinical features of enlargement of the thymus.

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The chief symptoms of thymic enlargement are those of tracheal stenosis. About this point has centred the controversy of more than half a century, a number of writers denying that any enlargement of the gland could exert such a pressure upon the respiratory passage. Numerous cases occurring in the literature of the last several years have proved beyond all doubt that such a compression of the trachea does occur as the result of thymic enlargement, even when the increase in size does not far surpass limits ordinarily regarded as normal. Percussion, radiography, intubation, and operation in the living subject have established the clinical entity of this affection, while certain modifications in autopsy technique have increased the amount of postmortem evidence supporting it.

Etiology.—In a small number of cases thymic enlargement is due to congestion and œdema resulting from acute infections, general circulatory disturbances, or, more rarely, trauma. In the majority of cases the enlargement is due to hyperplasia, and for this condition also it is very probable that there is a varied etiology. The primary cause may be sought in any infection, intoxication, or disturbance of metabolism in which there is a lymphoid or myeloid exhaustion. The enlargement of the thymus is, therefore, a secondary process of the nature of a compensation. In congenital syphilis and rachitis the thymic hyperplasia may with good reason be regarded as compensatory for the splenic fibrosis occurring in these diseases. In other cases we can only assume that the thymic enlargement is the result of some unknown lymphotoxic or myelotoxic condition. It is important to mention again in this connection the possible etiological relationship between adenoids and thymic hyperplasia.

Pathology.—As the clinical manifestations of thymic enlargement are pressure symptoms, it becomes necessary to include under this head all enlargements of the thymus due to any cause whatsoever (œdema, congestion, hyperplasia, new-growths, etc.). In the majority of cases the enlargement is due to a hyperplasia of some one of the histological elements of the organ, but particularly of the lymphoid tissue. In a general way all thymic enlargements may be classed as *relative* or *absolute*. Under the first are included all those cases in which the thymus fails to undergo its normal involution, so that there is found in the adult body a thymus either of the same size as the infantile gland or smaller ("persistence" of the thymus). The term persistent thymus is not a good one, since it has been found that thymic tissue persists normally to late adult life, and undoubtedly many cases reported in the literature as persistent thymus fall into the normal class. It is better, therefore, to regard all cases in which the thymus retains its infantile size beyond the normal period of retrogression as instances of relative hyperplasia or hypertrophy. The etiology, clinical and pathological significance of such cases are the same as those of absolute hypertrophy.

As absolute hypertrophy may be classed all enlargements above normal limits, either before the period of involution begins (end of second year) or after this time. The cases of "persistent thymus" in which the gland is larger than normal would, therefore, be brought under this head. Since in the majority of cases the enlargement is due to a numerical increase of some one of the histological elements, the term hyperplasia is preferable to hypertrophy. In the remaining cases the enlargement is the result of congestion, œdema, or new-growth. For all practical purposes it is more convenient to consider them together in this connection.

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As has already been stated, the weight of the thymus in different individuals varies greatly, even when the general conditions of the body are the same. Evidently no definite proportion exists between the weight of the thymus and that of the body as a whole. If we accept seven grams as the average weight in the newborn, and this is lower than the commonly accepted standards, we must bear in mind that an atrophic thymus may be heavier than this, owing to the fibrosis that may be present. Since there are so many conditions influencing the thymus weight, it would seem more expedient to base the diagnosis of thymic enlargement upon the dimensions of the organ rather than upon its weight. In general it may be said that any thymus weighing 15 grams or more is hyperplastic. In the average case of enlargement the weight runs from 15 to 50 grams, but instances of 150 grams have been recorded. Such weights are probably associated with neoplasms rather than with a simple hyperplasia. It must be emphasized that the postmortem size and weight of a thymus may be no index of its condition before death. A great enlargement due to congestion or œdema may wholly disappear at death, although it may have been the cause of a fatal stenosis of the trachea.

An increase in the thickness of the thymus is of far greater importance than an increase in any of the other dimensions. Grawitz, Pott, and others, have shown that the superior aperture of the thorax is a critical space, the trachea, œsophagus, great vessels, and thymus being contained within a space of about 2 cm. from the sternum to the vertebral column. In this space the thymus lies, applied directly against the anterior surface of the trachea. The sternum anteriorly and the vertebral column posteriorly form inflexible walls, so that an enlargement of the thymus to a thickness of 2½, 3, 4 cm. or more must be provided for by a diminution of the space occupied by the compressible structures lying in it. Such compression of the trachea has been shown to exist by means of the tracheoscope, by the relief afforded by intubation with a long tube, by operations reducing the volume of the gland, and by the autopsy demonstration of flattening, atrophy, and anæmia of the portion of the trachea lying in the superior thoracic strait.

As an argument against the possibility of compression of the trachea by an enlarged thymus gland, the statement of Scheele is frequently quoted. According to him, a weight of 750 to 1000 grams is necessary to compress the trachea of a child. Postmortem experiments of this kind cannot, however, be taken as an argument in favor of the view that an enlarged thymus cannot exert pressure enough upon the trachea to cause compression, inasmuch as we are in total ignorance of the actual amount of intrathoracic pressure produced during life by an enlarged thymus. That the degree of diminution of the mediastinal space is the important factor, and not the weight or dimensions of the thymus, is of course clearly evident.

That tracheal compression does result from thymic enlargement is definitely proved by numerous recently reported cases. Flügge found in 7 cases of sudden death in infants a marked compression of the lower portion of the trachea. Similar findings have been reported by other writers. On the other hand, such evidences of tracheal compression have not been observed in other cases of thymic enlargement, but this fact may be easily explained by the disappearance of the signs of compression after death. Biedert records an interesting case in which the exploration of the trachea by a catheter through a tracheotomy wound showed the presence of a marked stenosis, while at autopsy the examination of the trachea after the removal

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of the enlarged thymus showed no evidences of such a compression. The trachea of the young child is very elastic, and resumes its normal form as soon as any pressure upon it is removed. Therefore, in order to demonstrate at autopsy any tracheal stenosis resulting from an enlarged thymus, the neck organs should be examined before the thymus is removed. After the median incision has been extended upward over the larynx a subcutaneous dissection of the cervical fascia and muscles should then be carried out up to the floor of the mouth. The neck organs are then removed in the usual manner down to the clavicle, the œsophagus and trachea opened to this point, and the latter explored from above as far as the bifurcation. After the section of the cervical aponeurosis, the thymus, if hypertrophic, usually presents above the sternum as a pale, reddish-brown, spongy mass. Compression of the trachea by the enlarged thymus may also be easily demonstrated by fixing the neck and thorax of the child in formalin and alcohol before these regions are sectioned. These procedures should be carried out especially in medico-legal cases in which the cause of sudden death in infants or young children is sought. Hedinger has shown that a marked compression of the trachea may be demonstrated by the above method in cases in which the size of the thymus does not exceed the limits of weight and dimensions usually regarded as normal.

Thymic enlargement occurs as an apparently independent condition, or in association with the status lymphaticus, tonsillar hyperplasia, adenoids, rachitis, congenital struma, exophthalmic goitre, myxœdema, cretinism, acromegaly, myasthenia gravis, Addison's disease, epilepsy, congenital syphilis, scorbutus, leukæmia, anæmia, Hodgkin's disease, anencephaly, and the acute infections, or the enlargement of the gland may be due to a neoplasm developing within it. Excluding those conditions such as leukæmia, Hodgkin's disease, and lymphocytoma, in which the thymic enlargement is but a local manifestation of a disease process affecting all the blood-forming organs, there remains a group of cases constituting the great majority of thymic enlargements, and in these the thymus, on microscopic examination, is found presenting the appearances of a lymphoid hyperplasia. The acute enlargements occurring in association with the acute infections, particularly with diphtheria, etc., are due chiefly to congestion and œdema, but more or less lymphoid hyperplasia is usually associated with these.

The gross appearances of the hyperplastic thymus vary in different cases. As a rule, the main portion lies behind the upper part of the sternum, often extending more to the left of the median line than to the right, and downward over the upper third of the pericardium. The lower prolongations of the lobes may extend over the pericardium to the apex of the heart. The cervical prolongations of the lobes may also be hyperplastic. In a case of thymic stridor and sudden death occurring in a boy aged five years and a half, the hyperplastic cervical lobes extended to the floor of the mouth, the lower left lobe to the apex of the heart, the entire length being 18 cm. The main mass of the organ measured 7 x 5.5 x 4 cm. (See Plate X.)

The form of the hyperplastic thymus varies greatly. The anterior surface corresponds to the under side of the sternum and is usually convex; the posterior surface shows grooves and markings corresponding to the structures lying beneath. The hyperplastic lobes may be very nodular and tortuous. The color is usually pale pink or brownish red, the enlarged organ usually being paler than the normal thymus. On section the thymic tissue appears

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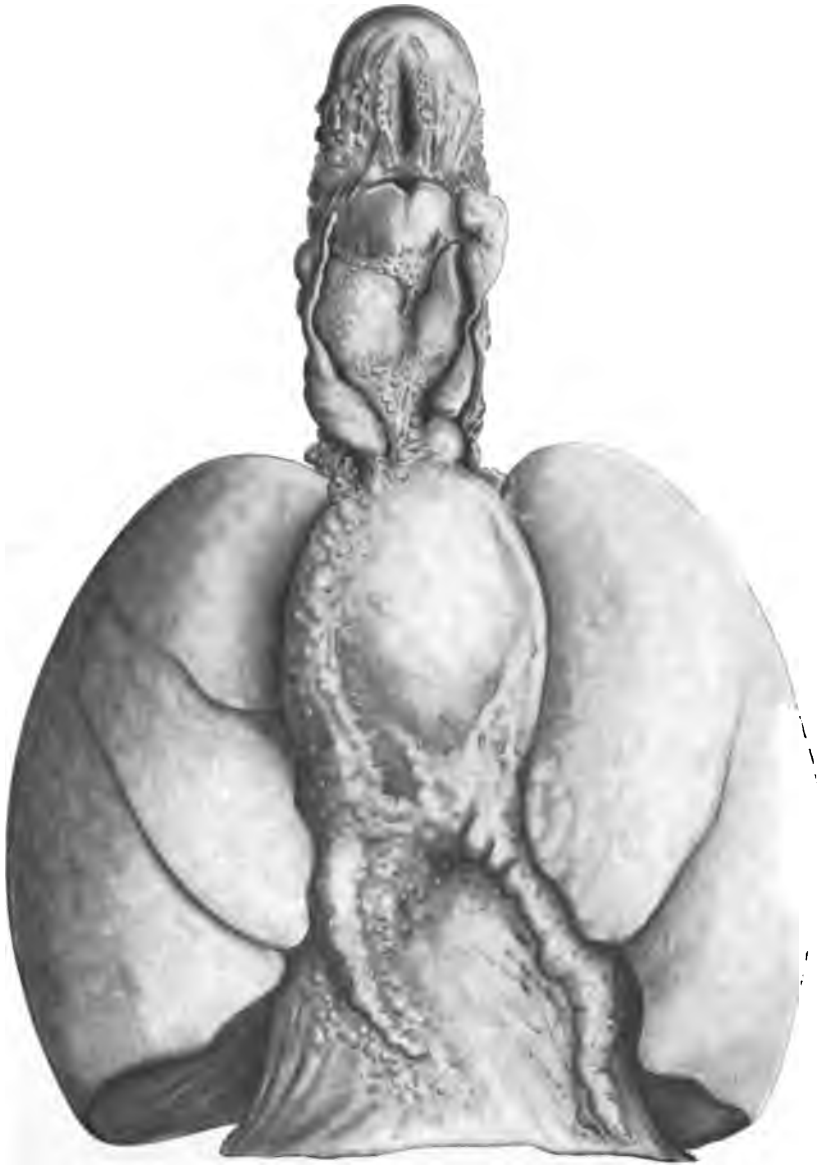
PLATE X



Hyperplastic Thymus from a Case of Thymic Death in a Boy Aged Five-and-a-half Years.

(Patient of Dr. D. M. Cowie. Autopsy by the writer.)

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nearly homogeneous; enlarged or cystic corpuscles of Hassall may appear throughout the cut surface as whitish or yellowish areas, in size about that of a pinhead or even larger. The consistency of the enlarged gland is usually softer than that of the normal thymus, and the postmortem softening of the central portion of the lobes is more marked and occurs more rapidly than in the normal thymus.

In the majority of cases of enlarged thymus the microscopic examination shows a lymphoid hyperplasia, with or without congestion and œdema. The general structure resembles the normal. The corpuscles of Hassall may appear more numerous and larger than in the normal gland. In patients older than two years the large size of the corpuscles forms one of the most striking microscopic features. In the glands showing passive congestion small hemorrhages may be present. The eosinophiles are usually increased and mononuclear eosinophiles may be present in large numbers. Smears from the cut surface may show the presence of myelocytes. Giant cells resembling those of the bone-marrow may also be present in the lymphoid tissue, particularly in the medullary portions about the trabeculæ and the corpuscles of Hassall. In some cases with definite symptoms of tracheal stenosis the thymus at autopsy shows no enlargement, and on microscopic examination appears perfectly normal. Such cases may be explained as due to transitory œdema or congestion disappearing after death.

The spleen and lymph glands may be either enlarged, of normal size, or atrophic. In each case the microscopic examination usually shows a lymphoid atrophy or exhaustion, with an absolute or relative increase in the stroma and a proliferation of the endothelial cells of the sinuses. The splenic follicles and the germ centres are reduced in number and size. The remaining ones may be made up chiefly of endothelioid cells. In the cases associated with congenital syphilis and rachitis the spleen often shows a marked fibrosis.

In two cases of thymic stridor and sudden death, with great hyperplasia of the thymus, the lymph glands were greatly enlarged, in one case giving the clinical picture of Hodgkin's disease, while in the other case the lymph glands were very atrophic. The spleen was greatly enlarged in the one case, moderately so in the second. The microscopic appearances of both spleen and lymph nodes were essentially the same in both cases. There was a marked disappearance of the lymphoid elements of the lymph nodes and spleen, the glands being made up almost wholly of tissue corresponding to hyperplastic stroma and endothelium. In the lymph glands germ centres were very few, and consisted chiefly of whorls of epithelioid cells. Similar changes were found in the Malpighian follicles. The bone-marrow in one case showed a lymphoid hyperplasia, in the other a lymphoid exhaustion. On the other hand the thymus of both cases presented the microscopic appearances of a lymphoid hyperplasia, with areas of myeloid tissue in one case.

It would seem not unreasonable to assume that in these cases there was a chronic infection or intoxication leading to a lymphoid exhaustion in the spleen and lymph nodes, followed by a proliferation of the stroma and endothelial cells somewhat resembling that seen in Hodgkin's disease. The hyperplasia of the thymus may, therefore, be regarded as compensatory in character. This is in accordance with Marfan's view of the compensatory nature of the thymic enlargement seen in association with the splenic

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fibrosis in congenital syphilis. The same thing may be said of thymic enlargement and splenic fibrosis in rachitis. In many cases observed clinically, thymic stridor disappears before the end of the second year, and the temporary enlargement of the thymus during the first two years of life may be interpreted as compensatory for deficient function of lymphoid tissue elsewhere, or to an excessive functional demand upon the lymph nodes, spleen, or bone-marrow.

In the majority of cases of thymic hyperplasia the general pathological picture is that of the so-called "status lymphaticus," but as has been mentioned above the hyperplasia of the spleen and lymph nodes varies in degree. All of the lymph nodes of the body may be hyperplastic or the hyperplasia may be confined to one or two glands. The intestinal, mesenteric, and retroperitoneal nodes are most frequently affected. The tonsils are nearly always enlarged and adenoids are usually present. But the significance of the status lymphaticus is that of the thymic hyperplasia which is present and is the cause of death. No line of separation can be drawn between the occurrence of thymic hyperplasia as a separate condition and that associated with hyperplasia of the lymph nodes. The microscopic changes occurring in the spleen and lymph nodes in status lymphaticus are essentially the same as those found in thymic hyperplasia without hyperplasia of the lymph nodes or spleen. All transition stages exist between those cases with atrophic lymph nodes and those with enlarged ones. In the early stages the spleen and lymph nodes may show a lymphoid hyperplasia, but in the latter stages the condition of these organs is that of a lymphoid atrophy or exhaustion with hyperplasia of the stroma and endothelium.

Evidences of compression by the enlarged thymus may be found in the trachea in the form of local anæmia, flattening, partial obliteration, atrophy of the tracheal wall, etc. The great vessels beneath the thymus may be compressed and the heart may be hypertrophied and dilated. Compression of the right ventricle has been observed, and thrombosis of the internal jugular vein, due to the pressure of an enlarged thymus. Evidences of asphyxia are always present; the general picture is that of death by suffocation, viz., congestion and œdema of the lungs and brain, atelectatic areas in the lung, chronic bronchitis, bronchopneumonia, subserous hemorrhages, cyanosis, etc. There is usually a marked postmortem hypostasis.

The body-fat is usually abundant and may be much increased. There is a more or less well-marked anæmia. The facies is frequently of the adenoid type, and the complexion pasty. Thickening of the skin, with œdema and eczema, may also be present. In the majority of cases there are rachitic changes, and evidences of congenital syphilis may be present. Hypoplasia of the heart and aorta has been observed, as well as aplasia and hypoplasia of the chromaffinic tissues. The thyroid is often enlarged. Hypertrophy and œdema of the brain have also been described in cases of enlarged thymus. Anomalies of the sexual organs are not infrequent. In cases of persistent thymus retarded sexual development is often seen. A condition of infantilism may persist after the age of puberty.

Symptoms.—The essential symptom of thymic enlargement is a respiratory disturbance resulting from the diminution of space in the superior thoracic strait. This respiratory difficulty may manifest itself in all possible grades, from a mild stridor to a very severe dyspnœa with fatal termination. In general there may be distinguished three classes of cases, falling under

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the heads of *thymic stridor*, *thymic asthma*, and *thymic death*. As this classification is based upon the degree of severity, there is, of course, every possible transition stage, and the more severe forms may at any time develop out of the milder. Nevertheless, this classification presents certain practical features, since some, perhaps many, cases never pass beyond the first or the second stages. Since the mechanical pathology of the condition has been demonstrated in so many cases, the term *thymic tracheostenosis* is preferable to thymic asthma and will probably replace the older designations.

Thymic Stridor.—In its mildest forms the chief symptom of thymic enlargement is a respiratory stridor resulting from tracheal compression. This is usually congenital or develops soon after birth. It is both inspiratory and expiratory, but is more pronounced during inspiration. The respiratory difficulty may be stationary or progressive, or the condition may manifest itself suddenly in its most marked form. In the latter case the attack may be precipitated by a prolonged fit of screaming or crying, particularly when the child's head is thrown backward. The stridor or the more severe asthmatic attacks may first appear during the course of some one of the acute infections, especially in connection with bronchitis, pneumonia, diphtheria, and whooping-cough. It is most probable that an acute congestion of the thymus lies at the foundation of these acute attacks and exacerbations. When the child is seen for the first time in such an acute attack, the diagnosis of diphtheria with laryngeal obstruction may be made and intubation or tracheotomy performed. No relief will be obtained from such procedures unless a tube long enough to pass the superior thoracic strait be introduced. The failure, therefore, to obtain relief by such treatment should lead always to a consideration of the possibility of thymic enlargement. The two conditions may, of course, be coincident, and the differential diagnosis must then be obtained through a consideration of the other features.

The thymic stridor is not accompanied by any modification of the voice. When severe, there is an inspiratory retraction of the thorax, most marked in the scrobiculus and suprasternal space. In the mild cases such a retraction is not seen. There is never any hoarseness in the uncomplicated cases. In its mildest forms the stridor is simply an audible respiratory sound perceptible at a slight distance from the patient. The greatest intensity is usually at the end of inspiration, but rarely the stridor is more marked during expiration, and is then usually interrupted and vibratory in character, resembling the clucking of a hen, flapping of a sail, etc. A distinctly rattling sound may sometimes accompany the breath sounds.

The intensity of the stridor varies greatly, from the faintest audible breathing to a loud sound that may be heard at some distance from the patient. It persists during sleep, but is usually weaker. It is either not affected or is improved by a horizontal position. Occasionally the stridor disappears for several minutes without any apparent cause. Its intensity is increased when the child is excited or crying, but it may be somewhat weaker immediately after a fit of crying or coughing. In the more severe cases there may be a more or less well-marked dysphagia. Otherwise the child may appear perfectly well or he may present some one or all of the general symptoms mentioned below.

Thymic Asthma (Kopp's Asthma).—The condition of thymic stridor as described above is frequently progressive, and shows a marked tendency to exacerbations of an asthmatic character, or severe attacks of asthma may

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occur in a child showing no previous symptom of stridor. Kopp first described the condition as "*asthma thymicum*," and his description is to be regarded as the classic one. The asthmatic condition may develop suddenly without previous symptoms, or may follow the condition of stridor. The first attack may be fatal, or there may be periodical recurrences of progressive severity. Twenty to thirty attacks or even more, may take place in the course of twenty-four hours. In general the symptoms of each attack are identical. The child throws the head backward with a marked inspiratory stridor, the face becomes anxious and cyanotic, then pale, the pupils dilate, the extremities are extended, and the hands clenched. Spasmodic attempts at inspiration occur, and the picture presented is that of an impending suffocation. To the signs of tracheal stenosis there may now be added the signs of laryngeal spasm. There is an inspiratory aspiration of the glottis and a descent of the larynx. With the closure of the glottis the heart sounds become very weak, the pulse cannot be felt, reflex irritability is lost, and death may take place within two or three minutes.

Not all patients die, however. The attack may subside quickly, and the child may, within a short time, resume his play free from all symptoms. In other cases the severe dyspnœa passes away, but a marked stridor persists. A pronounced dysphagia is present also in these severe cases. Repeated attacks of greater or less severity may follow the first. Recovery may be permanent or temporary, but in a large percentage of cases the condition is progressive until terminating in death.

Thymic Death (Mors Thymica).—Between thymic asthma and thymic death no sharp line can be drawn, but the latter term has come to be applied particularly to those cases in which death occurs suddenly without a definite history of previous respiratory difficulty. The distinction is one based solely upon the degree of severity. In those cases in which the child is found dead, the phenomena of thymic asthma may have preceded death, and in the other cases it is very probable that a careful examination before the fatal attack would have disclosed some evidences of tracheal obstruction. Nevertheless, in a certain proportion of cases an acute enlargement of the thymus due to a suddenly developing acute congestion brings on at once a laryngeal spasm and the child dies immediately.

The great point of interest is the cause of thymic death, and around this has been waged the controversy concerning the part played by the enlarged thymus, this condition being the essential pathological feature. Kopp pointed out clearly the etiological relationship of this enlargement to sudden death, but Friedleben and his followers denied wholly that thymic enlargement had any pathological significance. Nevertheless, Clar, Virchow, Cohnheim, and others conceded the possibility of an enlarged thymus producing dyspnœa through tracheal compression. Within recent years many writers have again asserted the direct etiological relationship between thymic enlargement and sudden death, and the cases reported by a large number of careful observers leave no doubt that thymic enlargement is the direct cause of death. As to the exact manner in which it is brought about there is still some question. All the symptoms and all the operative and postmortem evidence point to a suffocation resulting from tracheal stenosis and secondary laryngeal spasm as the chief if not the only cause of the fatal termination. To these may be added other effects of compression upon the heart, great vessels, vagi, and recurrent nerves. To a reflex spasm of the

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glottis may be added a reflex cardiac paralysis, or the latter may alone be the direct cause of death in those cases of sudden death in which all signs of tracheal compression or laryngeal stenosis are wanting. The direct action of the intoxication upon the heart or brain centres has also been regarded by some writers as a probable cause. The compression of the great vessels lying beneath the thymus may cause disturbances of blood pressure, cardiac dilatation, thrombosis, etc. The increased intracranial pressure and the marked tendency to œdema, so characteristic of thymic enlargement, may be the results of such vascular compression, and the laryngeal spasm and cardiac paralysis may be but the immediate results of a sudden increase of pressure at the base of the brain. The marked pulmonary œdema seen in many cases of thymic enlargement may be explained as the result of pressure upon the pulmonary arteries or veins. Zander and Keyhl have reported a case in which thrombosis of the internal jugular vein resulted from thymic compression, and a marked compression of the right ventricle has been elsewhere observed. There is, therefore, good anatomical evidence for some of these hypotheses. Nevertheless, an increasing number of reported cases reveal a pure mechanical pathology, *i. e.*, a thymic tracheostenosis sufficient in itself to explain all the clinical phenomena. For these cases, at least, theoretical and hypothetical arguments are no longer needed. Friedleben's dictum "Es giebt kein *Asthma Thymicum*" becomes a thing of the past.

We must, therefore, conclude that the immediate cause of death and the manner of death vary in thymic enlargement, but the general picture is that of a convulsive attack of thymic asthma of the severest type. The muscular spasm suddenly ceases, the face becomes ashy, then intensely cyanotic, the lips and tongue swollen and livid, reflex irritability is lost, there is rapid cardiac failure, and death suddenly ensues. Attempts at artificial respiration are followed by the evacuation of urine and fæces, but such efforts are without avail. The startlingly sudden character of thymic death, when occurring in a child previously in good health, gives to it a unique atmosphere of tragedy that not infrequently leads to medicolegal complications. This is particularly the case when the child is found dead in bed, the suspicion of intentional suffocation not rarely being unjustly aroused. On the other hand, it cannot be doubted that the diagnosis of thymic death, or "status lymphaticus," has been carried too far, and that many cases of genuine "overlaying" have escaped under this convenient disguise. All cases of this kind should be carefully examined according to proper autopsy methods.

The reported cases of thymic death tend to show that its occurrence is often apparently induced by a number of factors that have no effect upon the normal individual. Sudden death from fright or intense emotional excitement, during trivial surgical operations, anæsthesia, while bathing, swimming, etc., has in many instances been found to be associated with an enlarged thymus gland. It is probable that a large proportion of the deaths occurring in surgical anæsthesia are due to this condition. The fatal event may take place at any stage of anæsthesia, from the first whiff to several hours after the patient has recovered from the effects of the anæsthetic. Chloroform is usually regarded as the more dangerous anæsthetic in these cases. The manner of death varies, in some being very sudden, while in others there is a slowly progressive cardiac or respiratory failure.

An enlarged thymus has also been found in many of the sudden deaths

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associated with slight surgical operations, such as the extraction of a tooth, removal of adenoids or tonsils, circumcision, injection of curative sera, etc. In some of these cases anæsthesia was employed, and it is a question as to whether the anæsthetic or the shock of the operation is responsible for the death. Thymic death has also been coincident with the use of external applications. In a case seen by the writer the fatal attack of thymic asthma was apparently induced by a slight burn of the skin from a hot-water bag. A large amount of evidence has now been collected showing that cases of thymic enlargement are especially liable to sudden death while bathing or swimming. Many instances of sudden death from "cramps" while swimming have not shown the autopsy findings of drowning, but the presence of an enlarged thymus has been demonstrated. Cases of "found dead" in a bathtub also belong here, as well as those cases in which an accidental plunge into the water results in immediate death. Further, the frequent occurrence of thymic death in the acute infections, particularly in diphtheria, is a point of great practical importance, and the difficulty of differential diagnosis in the latter condition has been mentioned above.

Relation to Status Lymphaticus.—It is, of course evident that the condition of thymic death is that classed by many writers as the chief feature of the status lymphaticus. It is, however, a question as to whether the latter represents a definite primary pathological entity. It is much more probable that the clinical and pathological features usually regarded as characteristic of lymphatism constitute a cachectic complex secondary perhaps to a number of primary morbid processes, such as syphilis, rachitis, some latent infection, auto-intoxication, etc., that are characterized by an excessive demand upon the lymphoid and myeloid tissues of the body. At a certain stage in the process the lymph nodes may be enlarged, and it is to this stage that the term status lymphaticus is usually applied. The microscopic examination of the enlarged nodes may show, however, the same condition of lymphoid exhaustion found in those cases of thymic death in which the nodes are small. The thymic enlargement is most probably to be regarded as a purely compensatory condition secondary to some primary lymphotoxic or myelotoxic process. The sudden death in status lymphaticus is dependent primarily and wholly upon the thymic enlargement, and the latter condition becomes, therefore, the most important feature clinically. Moreover, thymic enlargement leading to thymic death may exist without any of the other clinical features ascribed to the status lymphaticus. Nevertheless, the latter term serves a very good function in designating the cachectic complex of thymic enlargement associated with adenoids, enlarged tonsils, enlargement of the superficial lymph glands, rachitis, etc.

Physical Signs.—Inspection.—The general appearance of the child or adult with enlarged thymus may be that of perfect health, but in many cases the complexion is pale, pasty, or muddy. During the attacks of asthma there may be marked cyanosis. Evidences of a mild grade of rickets are seen in perhaps the majority of cases. During the asthmatic attacks there may be a pronounced retraction of the interspaces and scrobiculus. The upper part of the sternum may be prominent, or the enlarged thymus may present as a distinct tumor in the suprasternal fossa, usually being most noticeable during expiration. A bulging of the upper part of the sternum has been observed in a number of cases. During forced expiration a portion of the thymic tumor may be forced through the superior thoracic strait

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PLATE XI

Case of Hyperplasia of the Thymus in a Boy Aged Five-and-a-half Years.

Marked suprasternal prominence. Thymic asthma terminating in thymic death.

(Patient of Dr. D. M. Cowie. Autopsy by the writer.)

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and present in the neck. A thymic tumor may present when the head is thrown back. Examination of the throat ordinarily reveals enlarged tonsils and adenoids.

Palpation.—The enlarged thymus may sometimes be palpated as an elastic soft tumor in the suprasternal fossa. The superficial lymph nodes may be more or less enlarged, and the spleen may be so large as to be felt below the edge of the ribs on deep inspiration.

Percussion.—The possibility of a practical percussion of the thymus has been ignored by the great majority of diagnosticians, hinted at by a few, and denied outright by others. Blumenreich and other observers have demonstrated its practicability. The former claims that light percussion, both in the living and in the dead child, will outline the thymic boundaries. The area of thymic dulness is triangular in shape, with unequal sides, the base at the level of the sternoclavicular articulation and the blunt apex above or behind the level of the third rib. The lateral boundaries extend somewhat beyond the sternal lines, usually somewhat more to the left than to the right. A small part of the thymus is covered by the anterior border of the left lung, but deeper percussion over this area will give a dull tone. On the right the area of relative dulness is very narrow, and is usually not taken into consideration. A thymus extending 2 cm. to the left of the median line will give on deep percussion an area of dulness extending 2 cm. to the left.

An area of dulness extending more than 1 cm. beyond the sternal lines may be taken as evidence of an enlarged thymus. In such cases the enlarged area may extend a little farther to one side than to the other, usually to the left. In children the thymic dulness is continuous below with that of the heart. In an adult with hypertrophic thymus the area of dulness may be continuous with the cardiac area, or may be separated from it by a zone of relative dulness or resonance of the width of an interspace or rib. In such cases the cardiac dulness is usually lower and farther to the left than normal. In Fig. 61 may be seen the area of an enlarged (persistent) thymus in an adult. Hochsinger has shown that the lateral boundaries of the enlarged thymus can be accurately determined by percussion, as shown by the coincidence of the percussion boundaries with the radiographic outlines. In 26 out of 58 children, Hochsinger determined by percussion an enlargement of the thymus, and was able to confirm it in all cases by the radiographic examination; 20 of these cases presented the symptom of congenital stridor. Ballin and others have failed to confirm Hochsinger's findings and oppose his views.

Percussion of the thymus from beneath while the child is held suspended face downward is also recommended, but this procedure is not necessary. In many normal children the thymic dulness disappears after the eighteenth month and sometimes even earlier. In general the area of thymic dulness may correspond to the area of dulness produced by tuberculous bronchial glands, as well as to that of aortic aneurism or mediastinal tumor. The differential diagnosis will rest upon the factors mentioned below. Percussion of the splenic area may reveal an enlargement of this organ.

Auscultation.—The most important auscultatory sign is the occurrence of an audible respiratory sound perceptible at a distance from the body, its greatest intensity being usually at the end of inspiration. When stronger during expiration, as occasionally happens, the stridor is interrupted and vibratory in character. It is heard distinctly all over the thorax, but is

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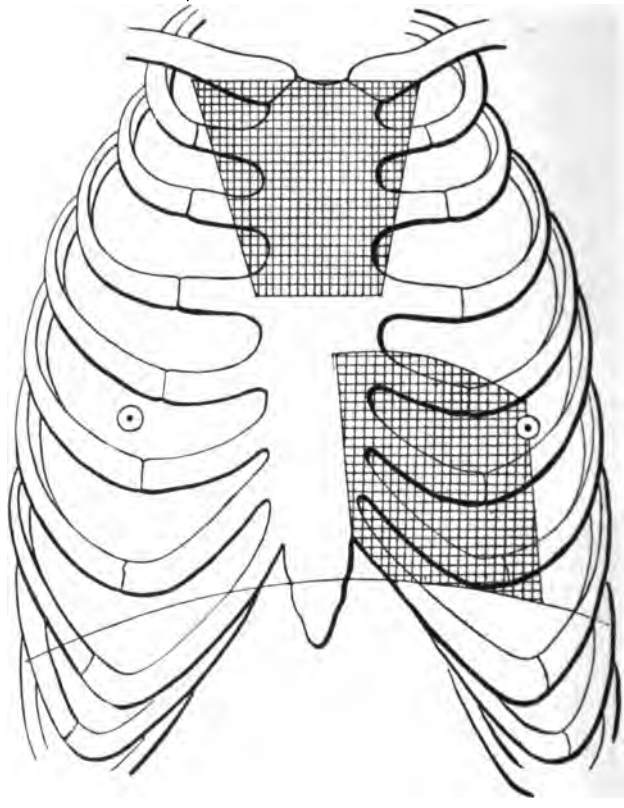
loudest over the upper part of the sternum. Its intensity varies greatly at different times. It persists during sleep and is not affected by a horizontal position. Occasionally it disappears for several minutes without any apparent cause. During the asthmatic attacks the stridor may be very intense. It is usually loudest when the child is excited or crying, but may be somewhat weaker immediately after. The voice sounds are not affected. There is no hoarseness, although a clear barking cough is sometimes present. As a complication, the auscultatory signs of a bronchopneumonia may be added.

FIG. 61



Percussion boundaries of "persistent" (relative hyperplasia) thymus in an adult.

Radiography.—The radiographic examination offers the most certain method of diagnosis of thymic enlargement. The child is laid flat upon its back on a flat-topped table. The plate holder containing the photographic plate is placed beneath the thorax of the child. The tube is held over the middle of the thorax at a distance of 50 cm. from the plate, and an exposure of thirty seconds is made. During the exposure the child must be held absolutely quiet and as flat as possible.

Radiographs obtained of apparently normal infants show some variation

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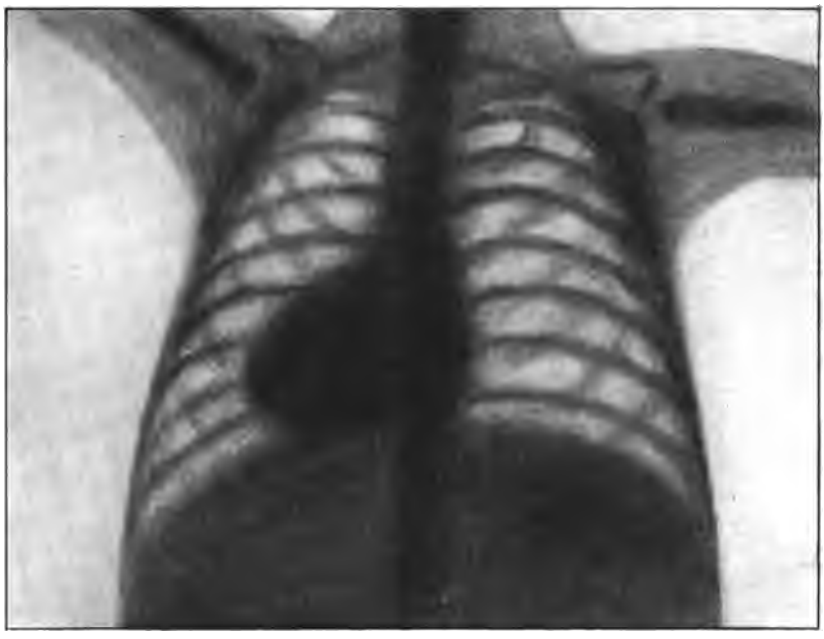
PLATE XII

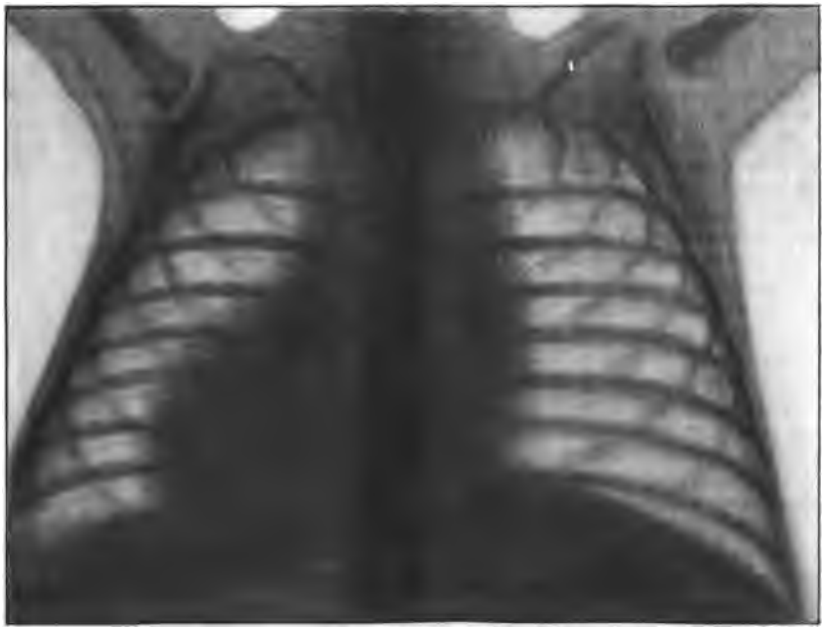
FIG. 1



Radiograph of Normal Child's Thorax.

Showing small thymic shadow with concave lines as it passes into the cardiac shadow.

FIG. 2



Radiograph of a Case of Hypertrophic Thymus with Stridor.

Large thymic shadow passing into the cardiac shadow by lines somewhat convex.

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in the size of the thymus within rather narrow limits. In the median line of the thorax there may be seen a flask-shaped shadow having a narrow neck and a plump body, the neck of the flask reaching from the first or second dorsal vertebra to the fifth or sixth. The body of the flask corresponds to the cardiac shadow, while the neck portion, whose lateral boundaries only slightly exceed those of the vertebræ, is the shadow of the thymus and great vessels. The neck portion of the shadow gradually broadens below with concave lateral margins, and in children the thymic shadow is usually confluent below with the cardiac, but occasionally a clear or lighter zone may be seen between the two shadows. (See Plate XII, Fig. 1.)

Under pathological conditions this median shadow is changed so that the neck becomes broader and confluent below with the cardiac shadow by convex lines instead of concave. (See Plate XII, Fig. 2.) In all of the 20 cases of thymic stridor examined by Hochsinger, the upper aperture of the thorax was filled with such a broad, plump shadow. The enlargement of the thymic shadow is often greater upon one side, more often upon the left, and this agrees with the autopsy findings of asymmetrical enlargement. It must be borne in mind, however, that an asymmetrical broadening of the thymic shadow may be produced by the child not lying flat. Proper attention to this point will, of course, prevent any distortion of the picture, but even if the child does turn during the exposure the plate can be properly interpreted, as the entire thoracic picture will be asymmetrical.

It should also be remembered that the shadows of heart and thymus are somewhat larger than the actual size of these organs, owing to the divergence of the rays and the distance between these organs and the photographic plate. Inasmuch as the radiogram gives no information concerning the thickness of the thymus, certain limitations in the application of radiography to the diagnosis of thymic enlargement are evident. A very thick gland not increased in length or breadth may give a small shadow while severe symptoms of tracheal compression are present. On the other hand, an organ increased in breadth and giving an enlarged percussion area and a broad shadow may not be increased in thickness, and pressure symptoms may be wholly absent.

The shadow of enlarged bronchial glands is different from that of the enlarged thymus in that it is most intense at the level of the root of the lungs and usually consists of a number of small spots at the sides of the base of the cardiac shadow, and lying so close to the latter as to appear as round convex protuberances.

Local Examination of Respiratory Tract.—A laryngoscopic examination can rarely be made during the severe attacks of thymic dyspnœa. In the milder cases, when carried out, it is with negative results; no abnormality of the larynx is found. The stenosis of the trachea or bronchus may sometimes be seen by means of a tracheoscopic or bronchoscopic examination. In very doubtful cases these methods should be used when possible. A low tracheoscopic examination (tracheotomy) is safer than the attempt to make a high examination. Intubation of larynx and trachea in the usual manner reveals no laryngeal stenosis and causes no amelioration of the symptoms, but intubation with a tube long enough to reach the bifurcation may give instant relief and establish the diagnosis of tracheal obstruction. When tracheotomy has been performed the trachea as far as the bifurcation may be explored and intubated through the tracheotomy wound.

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General Symptoms.—The blood may show a more or less pronounced anæmia and a relative lymphocytosis. Evidences of rachitis are present in many cases. The panniculus is usually abundant. Gastro-intestinal disturbances are not infrequent. There is a marked predisposition to catarrhal affections, tonsillitis, and adenoids. The general resistance is weak. The circulation is poor, and easily disturbed. A history of infantile eclampsia or idiopathic tetany is found in some cases, while in older patients attacks of dizziness and syncope are not uncommon. There appears also to be a definite association between thymic enlargement and epilepsy. In general, it may be said that the symptoms as a whole suggest a cachectic complex resulting from some intoxication or latent infection.

Diagnosis.—A congenital, chronic stridor, both inspiratory and expiratory, but most marked on inspiration, tending to exacerbations with the production of a dyspnœa so marked as to occasion intubation and tracheotomy and finally death, is usually due to thymic enlargement. The diagnosis may be easy when the thymus tumor can be made out by inspection, percussion, and Röntgen irradiation. In case this cannot be done various difficulties attend the diagnosis. Similar symptoms may be caused through tracheal stenosis due to mediastinal abscess, tumors, aneurisms, etc. Careful attention to all the physical signs will usually settle the question. Several other forms of stridor also occur in the newborn, and must be differentiated from that due to thymic enlargement.

The congenital stridor due to malformation of the vestibule of the larynx is purely inspiratory, the paroxysms are less grave and relieved by intubation with a short tube. The malformation may be determined by the examination of the larynx, and if it is not possible to do this with the laryngoscope the condition can be ascertained by a digital examination of the vestibule by one accustomed to intubation.

From the stridor caused by a compression of trachea or bronchi in the neighborhood of the bifurcation, as the result of pressure by enlarged or tuberculous lymph nodes, the thymic stridor can be distinguished by the fact that the former is purely expiratory, disappears during sleep, and diminishes when the child is inclined forward. It rarely appears before the fourth month, and as it is due to advanced tuberculosis of the bronchial glands in the majority of cases it usually precedes death by a few days only.

The stridor due to adenoids is distinguished by the difference in timbre and by its disappearance when the nostrils are closed, and the diagnosis may be readily determined by the examination of the nasopharynx. In the great majority of cases the symptoms, physical signs, and radiogram will establish the diagnosis beyond question. In rare cases without signs of tracheal stenosis the condition of thymic enlargement may exist without discovery until at autopsy, or even then may have subsided or disappeared so that the diagnosis fails entirely.

The tracheostenosis due to a spondylitic abscess may be distinguished with difficulty from that caused by an enlarged thymus. Hotz has reported a most interesting case of this kind, in which after the removal of the thymus, the tracheostenosis persisted and caused the death of the child. Such a persistence of symptoms after thymectomy would, of course, point to other complications; but the removal of the thymus is justified by the relief given to the intrathoracic pressure. Temporary improvement may result until other operative measures can be carried out.

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Prognosis.—In the present state of our knowledge it must be said that the prognosis in cases of thymic enlargement is in general grave. Since our conceptions of this condition, both clinical and pathological, are based almost wholly upon cases terminating fatally, we have no idea of the number of cases recovering. It is not at all improbable that many recover spontaneously. Those showing only the milder symptoms of stridor often recover after the second year, and recovery even from the more severe symptoms of tracheal stenosis has been observed. Avellis cites a case observed by Schmidt, of a woman aged twenty-five years, who had suffered from thymic asthma as a child, and who still after any overexertion exhibited symptoms of obstruction of the respiratory passage. A laryngoscopic examination revealed a tracheostenosis. There is every reason to believe that with early diagnosis a fatal termination may be avoided in many, if not the great majority, cases of thymic stridor and asthma. With intubation by a long tube offering immediate although temporary relief, and the possibility of a permanent cure through operation, the outlook is not so discouraging as it has been regarded. At the same time it must be remembered that the prognosis in all cases of thymic enlargement becomes very grave in the case of intercurrent infections, operations requiring anæsthesia, etc. Even the throwing of the head far back is sufficient to cause thymic enlargement and to set up a vicious circle that may lead quickly to suffocation. Children showing evidences of thymic enlargement, even in its mildest manifestations, should be guarded with extreme care.

Treatment.—The treatment of enlargement of the thymus resolves itself along two lines: the prevention of thymic asthma and operative treatment in case the tracheal compression becomes so marked as to endanger life.

Preventive Measures.—Since the dangerous feature of thymic enlargement is suffocation resulting from the pressure of the enlarged gland upon the important structures lying beneath it, special care should be taken to avoid all conditions by which any increase in the volume of the gland might be produced.

1. *Position.*—A child having a large thymus should not be allowed to throw the head far backward. A high position of the head should be maintained, even if it is necessary to use special apparatus for this purpose. Some children do better when kept in a horizontal position, the stridor becoming worse when sitting.

2. *Avoidance of Excitement.*—Such children should be kept as quiet as possible. Attacks of crying or screaming, or of strong emotional excitement should be avoided. Excessive exercise, running, leaping, etc., should be prohibited.

3. *Operations.*—Surgical operations, especially those requiring anæsthesia, are attended by unusual risks in cases of thymic enlargement. Should such an operation become absolutely necessary, the situation should be fully explained to the parents and all preparations made for a possible tracheotomy and intubation of the lower portion of the trachea. Even with such preparations the suddenness with which thymic death may occur will in a certain proportion of cases render the precautions of no avail. The emotional excitement aroused by an attempt to make a laryngoscopic examination may precipitate the fatal attack of asthma with spasm of the glottis and immediate death. Anæsthetics must be administered with the greatest pre-

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cautions. Tracheotomy should be done under infiltration anæsthesia, and in the case of an operation upon the thymus, chloroform may be given through the tracheal cannula.

4. *Bathing.*—Very warm or cold baths are to be avoided. Thymic suffocation has been known to follow immediately the shock of immersion in hot and cold baths. Children or adults with enlarged thymus should not be allowed to go swimming or bathing.

5. *Prevention of Infection.*—Acute infections, particularly those involving the upper respiratory tract and causing thymic congestion (diphtheria, bronchopneumonia, whooping-cough, etc.) are especially likely to excite attacks of thymic asthma that may end fatally. Unusual care should, therefore, be exercised in the protection of children having large thymic glands from the possibility of acute infections.

6. *General Hygiene.*—The general hygienic treatment should be such as to increase the general metabolism of the body and its resistance to infection. The diet should be carefully regulated. Treatment for syphilis or rickets should be carried out if necessary, and particularly should attention be paid to the excretory organs. A quiet out-of-doors life in a good climate should be advised when possible. If the thymic enlargement is the result of a compensatory hyperplasia for an excessive drain upon the lymphoid tissues, the general hygienic treatment should be that of general marasmus due to chronic intoxication or infection. Catarrhal affections of the upper respiratory tract, adenoids, enlarged tonsils, should be carefully treated.

Curative Treatment.—In those cases of thymic stridor or asthma in which there is marked dyspnœa with apparent danger of suffocation more radical treatment is demanded. This represents a recent advance in clinical medicine, since in the text-books of a few years ago and in the majority at the present time no hint is given of any possible line of therapy for this condition.

1. *Intubation.*—The introduction of a tube long enough to reach the bifurcation of the trachea may bring about immediate amelioration of the symptoms and may save the child's life during a severe attack. Such a case has recently been reported by Marfan. Intubation with a short tube or the performance of tracheotomy is of no avail in thymic stenosis of the trachea. In the latter case the symptoms may be relieved by the introduction through the tracheotomy wound of a tube long enough to reach the bifurcation. The relief thus afforded may be only temporary as the symptoms of suffocation may follow the removal of the tube.

2. *Röntgen Irradiation.*—The selective action of Röntgen rays upon lymphoid tissues would indicate their employment in cases of hyperplastic thymus in the hope of reducing the volume of the enlarged organ. In one of the cases reported by Hochsinger there was a decrease in the area of thymic dulness and an improvement in the stridor after repeated exposures. The child, however, was syphilitic and was receiving antisyphilitic treatment at the same time, so that the part played by the rays cannot be absolutely determined. From the results of experimental investigations as to the action of Röntgen rays upon lymphoid tissues there can be but little doubt that prolonged irradiation would reduce the size of the enlarged thymus. There are, however, other considerations to be regarded as far as this form of treatment is concerned. The action of Röntgen rays in inhibiting further growth in the tissues of young animals exposed to their action, as well as the possi-

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bility of the production of an intoxication from the products of lymphoid disintegration must be borne in mind as possible dangers of this treatment. For various reasons, based upon recent studies of the changes produced in the tissues by the Röntgen rays, their use in the treatment of enlarged thymus must be advised with caution.

3. *Antisyphilitic Treatment.*—If, as appears in some cases (Marfan's, Hochsinger's), the hyperplasia of the thymus is secondary to syphilitic fibrosis of the spleen, it might be well in all doubtful cases to carry out antisyphilitic treatment. Both Hochsinger and Marfan have reported decided improvement to result from such treatment.

4. *Treatment for Rickets.*—The frequent association of rickets with enlarged thymus is sufficient reason for treating it in all doubtful cases.

5. *Operation.*—To the development of thymic surgery we must look for the most brilliant results in the treatment of hyperplasia of this organ. The pioneer work has been done, the possibility is proved, and the path pointed out. The first operation upon enlarged thymus was performed by Rehn, Jr., and described by Siegel. A child, aged two and a half years, suffered from extreme dyspnœa and attacks bordering upon suffocation. A clinical diagnosis of laryngismus stridulus was made and tracheotomy done without any relief. The insertion of a long cannula through the tracheotomy wound reaching to the bifurcation gave immediate relief to the symptoms. When, four weeks later, a shorter cannula was introduced, the dyspnœa returned. In consequence a clinical diagnosis of mediastinal sarcoma or thymic hyperplasia was reached, and it was decided to perform a radical operation. An incision was made in the median line in the suprasternal depression, and an enlarged thymus was revealed. This was drawn out as far as possible and stitched to the fascia over the sternum. A permanent cure resulted. A second case was soon afterward operated upon by König, the patient being an infant nine weeks old, suffering from the second week with severe dyspnœa. A soft tumor was found presenting in the suprasternal depression. This was diagnosed as an enlarged thymus. It was exposed by a median incision, drawn outward from the neck organs, partly resected, and in part fastened to the manubrium. This operation likewise gave a permanent cure. Biedert cites a similar case seen by Perrucker.

A more recent case is that reported by Theodor and Ehrhardt. A child, aged two years, of healthy parentage, and showing no evidences of rickets, developed a progressive stridor and dyspnœa, increasing in severity until occasional attacks of partial suffocation occurred. There was marked inspiratory stridor with cyanosis and inspiratory retraction of the jugular fossa and epigastrium. No physical signs of an enlarged thymus could be made out. The percussion of the thymic area was negative. Intubation of the larynx was easily accomplished, but did not affect the dyspnœa. This, however, determined the diagnosis of tracheal stenosis, and operation was advised. A median incision about 6 cm. long was made extending 1 cm. downward over the manubrium. The isthmus of the thyroid was cut and the trachea laid bare. At every expiration a large part of the thymus gland with its two upper poles presented in the suprasternal space. It was seized and gradually drawn outward and enucleated without difficulty. The trachea as far as the bifurcation was then exposed and found to present a distinct flattening. Respiration at once improved, but the wound was not

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closed for several days for fear of a return of the symptoms. When finally closed a complete and rapid recovery resulted. The thymus after removal measured 5 cm. in length, 4 cm. in breadth, and 2 cm. in thickness. Microscopic examination showed only the appearances of a normal thymus.

The seventh operative case is an American one, the operation having been performed by C. Jackson, of Pittsburg. A boy, aged four years, gave characteristic signs of thymic tracheostenosis. By means of the tracheoscope introduced through a tracheotomy wound, the trachea was found to be obstructed to such an extent that the walls were almost in contact. Symptoms were relieved by the passage of a long tracheal cannula. An almost complete thymectomy was performed with perfect cure.

The experience of these operators agrees as to the ease of the operation and its freedom from technical difficulties. As to the ligation of the thymic vessels, Ehrhardt compares the operation to the extirpation of a large mass of lymph nodes. Since in many cases the tracheal flattening is a chronic condition, there is some danger that the normal shape of the tracheal lumen may not be resumed immediately after the removal of the thymus, hence Ehrhardt's precaution in keeping the wound open for several days is wise. The fact that so few operations upon the thymus have been performed may be explained by the rarity of diagnoses of enlarged thymus during life. There is, however, every reason to believe that with the development of thymic percussion and radiography an increased number of thymic enlargement should be diagnosed and operated upon, and the mortality of thymic enlargement and the status lymphaticus be correspondingly reduced. In the case of young children, resection of the thymus or stitching it to the sternum is advised rather than extirpation, bearing in mind the possibility of the effects of thymic function upon the development of the bones and sexual organs. The child operated upon by König developed a florid rachitis and did not walk until after four years of age. At the Surgical Congress in 1906, he advised against a complete thymectomy, and recommended that the organ be drawn out, resected, or stitched to the sternum.

General Treatment.—During the attacks of thymic asthma, hot or cold applications may be made to the neck and upper part of the sternum. Laxatives should be freely employed. Cardiac stimulants may be given when the asthmatic attacks are very severe. The threatened suffocation may also be averted by the use of oxygen. Still, all these measures are but temporary expedients, and unless relief is marked, intubation with a long tube should be carried out and the radical operation performed as soon as possible. Thymus feeding is apparently without effect upon the enlarged gland, but seems to have a general tonic action, so that its employment may be worth while.

INFLAMMATION OF THE THYMUS.

Thymitis.—Acute inflammatory processes are apparently very rare, but thymic abscesses, either single or multiple, have been reported as occurring in association with Ludwig's angina, pericarditis, pleuritis, pyæmia, etc. Extreme caution is necessary in the diagnosis of thymic abscess at autopsy that no mistake be made in the interpretation of the thick, pus-like fluid found postmortem in the normal organ. It is very probable that the

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majority of the reported cases of thymic abscess are in reality based upon such misinterpretations. Especially is this probable when after the sudden death of a child the only pathological lesions found were small, single, or multiple thymic abscesses. There can be but little doubt that the so-called abscesses of Dubois are in the majority of cases the result of a postmortem softening of the medullary portion of the thymus, and in other cases the result of a proliferation and subsequent degeneration of lymphoid cells in the corpuscles of Hassall. They must, therefore, be carefully differentiated from true thymic abscesses. A critical survey of the literature leads us to reject practically all cases reported under this head. The case reported by Pürkhauer of a four-year-old boy dying suddenly while in apparently perfect health, and showing at autopsy a thymic abscess that had ruptured into a bronchus, appears to be a true instance of thymic abscess. Less uncertainty is attached to the recent case of Dudgeon. In the right lobe of the thymus of a child dying suddenly a large abscess cavity containing pneumococci was found. With the exception of a slight degree of rickets, no other pathological conditions were discovered.

Of acute or chronic non-suppurative forms of thymitis practically nothing is known. The fibroid changes described by Jacobi and others as analogous to the chronic interstitial inflammations of liver or kidneys may very well have been nothing more than the fibrous changes of primary or secondary thymic atrophy, and not inflammatory in origin. The cases of chronic thymitis reported in the older literature are all very doubtful, and probably represent a variety of conditions. With so few reliable observations of inflammatory conditions of this organ, we are in practical ignorance of their etiology, occurrence, and significance.

TUBERCULOSIS OF THE THYMUS.

Primary tuberculosis of the thymus is apparently of very rare occurrence, judging from the paucity of recorded observations. The majority are, moreover, open to doubt, particularly those in the older literature. Care has not always been taken to differentiate the superior mediastinal lymph-glands from the thymus, and the latter organ has, no doubt, often been incorrectly included in the tuberculous mass arising primarily in these glands. Moreover, the same mistake has been made in this connection as with reference to the occurrence of gumma and abscess in the thymus, the physiological collections of thick fluid found in the organ having been also misinterpreted as caseous tubercles. Although Pürkhauer and others of the older writers regarded the thymus as a frequent seat of the primary focus in general miliary tuberculosis of children, the recorded observations are wholly unsatisfactory and inconclusive, and are for that reason rejected. The only observation of undoubted primary thymic tuberculosis appears to be the case reported by Demme. A child of non-tuberculous parents died in the third month of general marasmus, the only physical sign being some dulness over the manubrium sterni. The autopsy showed an enlarged thymus gland containing several typical tubercles with tubercle bacilli. No other evidences of tuberculosis were found in the body.

Secondary tuberculosis of the thymus is also rare, but a number of cases have been reported. Friedleben found tubercles in the thymus in 3 of

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73 cases of general tuberculosis, all being in early childhood. Jacobi saw three cases of secondary thymic tuberculosis in infants associated with general tuberculosis. Pust has analyzed 12 cases of secondary tuberculosis of the thymus seen in the Pathological Institute at Kiel during the years 1875 to 1902, 3 of these cases being in adults. Dudgeon records 4 cases in which the thymus was involved. In addition, there is a small number of isolated observations of thymic tuberculosis associated with general or thoracic tuberculosis. From the collected cases we find that secondary tuberculosis may occur in the form of miliary tubercles, larger caseating tubercles, or the thymus, in part or in whole, may be converted into a fibrocaseous mass. The great majority of the cases occur in early childhood, and the condition has been discovered only at autopsy. No symptoms referable to the involvement of the thymus have as yet been recorded. In the case of large caseating masses replacing the thymus, dulness over the manubrium sterni would be found on percussion, and it is possible that pressure symptoms might be produced. A clinical differentiation between thymic tuberculosis and tuberculosis of the superior mediastinal glands would appear at the present to be impossible. Moreover, a pathological diagnosis of thymic tuberculosis cannot be made positively without the demonstration of the presence of undoubted thymic elements in the tuberculous tissue. Since the superior mediastinal lymph glands are practically always involved in advanced cases of general thoracic tuberculosis in children, and form large fibrocaseous masses adherent to the neighboring structures, it may be easily assumed that the thymus is involved, whereas in the majority of cases it is pushed to one side and is atrophic. The diagnosis of thymic tubercle should, therefore, rest upon the microscopic examination.

SYPHILIS OF THE THYMUS.

Numerous statements occur in the literature concerning changes found in the thymus as the result of congenital syphilis. Hyperæmia, hemorrhage, fibroid changes, thickening of the vessel walls, abscesses, cysts, etc., have all been ascribed to the action of syphilis upon this organ. It has even been affirmed by some writers that the thymus is the first organ to show the effects of congenital syphilitic infection, while others state that it may be the only organ in the body to show such changes. An analysis of the varied pathological conditions of the thymus ascribed to syphilis leaves practically nothing that can be said positively to be the direct result of congenital syphilis. As in the case of the "abscesses" described by Dubois, the majority of the supposed syphilitic conditions of this organ are nothing more than changes occurring constantly as a part of the normal retrogression of this organ, and may be seen in any thymus. While there is no reason to believe that the thymus should escape involvement in syphilis, up to the present time no indubitable evidences of such special involvement have been presented. While a marked atrophy and fibrosis of the thymus may be seen in infants having congenital syphilis, these conditions are to be connected with the marasmus produced by the disease rather than to any specific local action. Precisely similar changes may be found in any form of infantile marasmus.

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THYMUS IN OTHER DISEASES.

Acute Infections.—In children dying from acute infections the average weight of the thymus is found to be less than normal (Dudgeon). As the body weight is also diminished, a corresponding diminution in the thymus weight would be expected. An exhaustion of the lymphocyte-forming tissue may also aid in bringing about such a loss of thymic substance. Congestion of the gland persisting after death will increase the weight and dimensions of the organ, but after the blood is out of the organ these fall below the normal. Careful studies of the part which the thymus plays in acute infections and intoxications are much needed, particularly with reference to the role of the lymphocytes and eosinophiles. Small hemorrhages throughout the tissue of the thymus are common in those cases of acute infection accompanied by lobar or bronchopneumonia. A marked passive congestion of the organ as a whole is constantly associated with these conditions. The other conditions described in the literature as occurring in connection with the acute infections, viz., fibrosis, liquefaction, necrosis, degeneration of Hassall's corpuscles, etc., are for the greater part based upon misinterpretations of physiological or postmortem changes. In the latter class belong most probably the areas of karyorrhexis and necrobiosis described by Jacobi as occurring in the thymus in cases of diphtheria. Likewise, the observation made by Acland of peculiar changes found in the thymus in hæmophilia and purpura is very doubtful.

Graves' Disease.—A relation between the thymus and thyroid has been affirmed by several writers. The fact that in this disease the thymus has usually been found to be persistent or hypertrophic has been taken as a basis for the assumption that there is some correlation of function between the two glands. The microscopic examination of the enlarged thymus found in cases of exophthalmic goitre shows no changes that can be regarded as essentially pathological beyond a simple hyperplasia. Enlargement of the thymus has also been observed in *myxœdema, myasthenia, Addison's disease, rachitis,* etc. Further, thymic hyperplasia has been noted as occurring in certain forms of *acromegaly* associated with enlargement of the hypophysis. Klebs has attempted to explain the giant growth by a theory of angiomatosis resulting from overfunctional activity of the thymus. No pathological foundation exists in support of such an hypothesis.

Cysts.—Through the retrogression of Hassall's corpuscles small cysts filled with a pus-like fluid (so-called "abscesses of Dubois") are formed in practically every thymus. They are usually of the size of a pea, but may be much larger. The cyst wall consists of a stratified, flattened epithelium, while the contents are made up of lymphoid cells that have either proliferated or migrated into the corpuscle and there undergo softening. These cysts have no relationship with syphilis or other pathological conditions. The larger areas of softening often seen in the centre of each thymic lobe have also been classed with the abscesses of Dubois. They are due to a postmortem softening or digestion of the lymphoid tissue. Definite cavities filled with a thick, yellow, pus-like fluid, often blood-stained, are thus formed. On microscopic examination the fluid is found to consist almost wholly of lymphocytes showing fatty droplets, karyorrhexis, etc. In all cases of apparent abscess, cyst formation, suspected gumma, etc., a careful

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microscopic examination should be made in order to differentiate them from the above conditions.

Tumors.—Neoplasms arising primarily in the thymus are rare; and, further, many of the tumors reported as originating in this organ were most probably primary in the mediastinal lymph nodes. Positive proof of the primary thymic origin of a tumor lying in the superior part of the anterior mediastinum must be sought in the demonstration of the presence of Hassall's corpuscles. In case the mediastinal lymph nodes are found not to be involved in any given case, it may be assumed that any tumor lying behind the upper portion of the sternum most probably arises from the thymus or its remains (Letulle's criterion). This, however, is not a very safe criterion, and the critical survey of all the cases reported as primary in the thymus leaves few that can be properly regarded as having such an origin.

Of the tumors reported as occurring in the thymus region, the most common form appears to belong to the group of closely related neoplasms embracing the *lymphoma*, *lymphadenoma*, and *lymphosarcoma*. Into this group fall also the tumor-like hyperplasias of the thymus seen in *pseudoleukæmia* and *leukæmia*. There can be little doubt of the close genetic relationship existing between such lymphoid tumors and the leukæmias, and, following the plan adopted under tumor of the lymph nodes, the lymphoid tumors of the thymus may be divided into two classes, the *aleukæmic* and the *leukæmic lymphocytomas*. In the first class would fall the various forms of *round-cell sarcoma*, *lymphosarcoma*, *lymphoma*, and *lymphadenoma* without a coincident leukæmic condition of the blood; into the second class, the *lymphoid tumors of the thymus associated with leukæmia*. In leukæmia the thymic tumor may be a secondary localization, or it is possible that there may be a primary thymic leukæmia. Cases recently reported under the head of *leukæmic thymus sarcoma* may represent this condition. The lymphoid tumors are usually the manifestations of a general disease, and are therefore malignant, hence their classification into benign (lymphoma, lymphadenoma, lymphocytoma) and malignant (lymphosarcoma), while based upon local histological characteristics of the tumors, gives a false conception of their nature. It is also possible that myeloid tumors may be found in the thymus, with or without a coincident leukæmia. It has been stated that the lymphoid tumors primary in the thymus form diffuse masses, while those primary in the mediastinal lymph nodes are nodular. The tumor on section shows the smooth homogeneous surface characteristic of the lymphoid tumors found elsewhere.

Medullary and *hemorrhagic round-cell sarcomas* have also been described as originating in the thymus, but are very doubtful. They probably belonged to the class mentioned above. The *lipomas* and *lipogenic sarcomas* found in the upper anterior mediastinum are also of doubtful nature. The fatty tumors probably represent a local lipomatosis following thymic atrophy.

Primary carcinoma of the thymus has also been reported. Such an occurrence could be explained by the origin of the carcinoma from the epithelial elements of the organ or from included epithelial structures. *Secondary carcinoma* has also been reported, but some of these cases were undoubtedly instances of metastases in the mediastinal lymph nodes.

Teratomas and *dermoid cysts* of the thymus have also been recorded. The latter take their origin from epidermal inclusions or arise from bigerminal implantation, or from persistent epithelial anlage. The writer has seen a

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malignant teratoma of the thymus region containing multiple dermoid cysts, and giving rise to carcinomatous metastases over the pericardium and heart. Lymphoid hyperplasia of the gland is usually associated with the dermoid cysts of this region.

Symptoms.—The symptoms of primary thymic tumor are in general the same as those belonging to the neoplasms of the anterior mediastinum. The sternum may be arched or eroded. On percussion an area of dulness over the manubrium may be made out. Pressure symptoms, such as stridor, asthma, cough, hoarseness, laryngeal spasm or paralysis, etc., may be present. The asthmatic attacks may end fatally. In the case of mediastinal dermoids the trachea or bronchus may be eroded and hairs may be expectorated. The radiogram may reveal the shadow of the tumor.

Treatment.—Röntgen irradiation may be tried as a last resort. In the case of the lymphoid tumors the tumor may become greatly reduced in size. The only hope of a permanent cure, however, lies in surgical operation and removal of the neoplasm.

THYMUS THERAPY.

Naturally the thymus would suggest itself as offering a proper field for experimental work along the lines of organotherapy, and many clinical investigations have already been carried out in this direction, but without as yet giving much hope of their being of any practical value. The administration of thymus gland has been carried out in exophthalmic goitre, simple goitre, myxœdema, acromegaly, Addison's disease, etc., and the results obtained are conflicting. Good results have been claimed in simple goitre and Graves' disease, but some of the most recent work with the latter disease tends to show that the treatment has no effect upon the goitre, heart, or exophthalmos, but appears to possess some value in improving the general condition. Good results have also been claimed for thymus feeding in rickets, and it might be well to try it in cases of thymic enlargement and status lymphaticus or infantile marasmus. On theoretical grounds, thymus feeding might be used in cases of precocious development. Fresh raw mutton thymus may be used, or tablets prepared from such; 10 to 25 grams are given daily. No ill effects have been observed in connection with such treatment.

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CHAPTER XIX.

DISEASES OF THE LYMPHATIC GLANDS.

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General Considerations.—The great majority of the diseased conditions of the lymphatic glands are *secondary* in nature, and are the direct result of the part played by the lymphoid structures in the protection of the body. In the exercise of their function as *filters* of the lymph stream, whereby they remove from the latter both the bland and harmful substances gaining entrance into the lymphatic vessels, their own integrity is often sacrificed to the welfare of the organism as a whole. Into the lymph stream of any region of the body a great variety of formed elements may pass, such as dust, carbon, bacteria, disintegrating red and white blood cells, blood pigment, dead-tissue cells, inflammatory exudates, tumor cells, toxic substances, etc. Usually the regional lymph nodes filter out such foreign substances and retain them either permanently or temporarily, in some cases rendering them harmless or destroying them, while in other cases the injurious agent is able to cause degeneration or necrosis and inflammation within the lymphoid tissue itself. In this conflict, particularly when pathogenic bacteria are concerned, the lymphatic glands may suffer severe inflammatory processes, even to the extent of total destruction by suppuration; but in the great majority of cases the infective agent is disposed of by the gland after a more or less marked local inflammatory reaction. *Lymphogenous lymphadenitis* due to local primary infections, becomes, therefore, the most important and common affection of the lymphatic glands.

Since the involvement of the regional lymph glands is usually secondary to some primary infection within the region tributary to them, we find, for example, involvement of the axillary and cubital glands in the case of infections of the hand, arm, or mammary gland, involvement of the cervical glands in infections of the mouth cavity and pharynx, of the bronchial glands in pulmonary infections, of the mesenteric glands in intestinal diseases, of the inguinal glands in infections of the external genitals and lower extremities, etc. Such an involvement of the regional lymph glands occurs also in chronic inflammations of the corresponding regions and in the case of malignant tumors occurring therein, particularly carcinoma.

Hæmatogenous secondary affections of the lymphatic glands also occur, but are relatively much less frequent than the *lymphogenous* conditions. Multiple or universal involvement of the lymph glands characterizes the hæmatogenous affections, whereas in the lymphogenous conditions one set of regional lymph glands is usually alone involved. The infective agent reaches the glands through the arteries, and the localization in the lymphatic glands is but an expression of a generalized process. Such hæmatogenous affections of the lymphatic glands are seen in the secondary stage of syphilis, in anthrax, diphtheria, and a number of other of the infectious diseases;

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indeed, hæmatogenous lymphatic involvement may occur in practically every one of the infectious diseases as a not infrequent condition.

The *primary* diseases of the lymph glands are relatively rare compared to the secondary ones. With the exception of cryptogenic primary infections, they consist almost wholly of *hyperplastic* and *tumor-like* conditions showing a more or less malignant and progressive course. They may involve all the lymph glands of the body, or only regional groups. Their clinical classification is confused, their etiology unknown, and different authorities are not agreed as to their pathological nature. To this class of primary lymphatic affections belong the various conditions of the lymph glands known as Hodgkin's disease, adenia, lymphadenia, lymphogenic diathesis, lymphadenosis, lymphoma, lymphocytoma, lymphomatosis, pseudoleukæmia, leukæmic and aleukæmic lymphoma, lymphosarcoma, etc. Primary tumors of the lymph glands of a type other than that of the lymphoma or lymphosarcoma are very rare.

INFLAMMATION OF THE LYMPH GLANDS. LYMPHADENITIS.

Lymphadenitis Simplex.—In the majority of cases inflammation of the lymph nodes is the result of the entrance of bacteria or of poisonous substances into the afferent lymphatics. There is usually an associated lymphangitis, but it may be of so slight a degree as to pass unnoticed. While the condition of lymphogenous lymphadenitis is more often localized in a regional group of glands, the entire lymphatic system may be affected in cases of generalized infection or intoxication, and in such cases the inflammation is usually hæmatogenous in origin. Trauma alone has been thought to be sufficient to cause inflammation of the regional glands of the part or extremity involved, but in such cases infected scratches or cuts are usually present, or cryptogenic infection has occurred. Direct injury of the nodes is a relatively rare cause of lymphadenitis. On the other hand, no evidences of lymphadenitis may be found in the regional glands of an extremity showing ascending gangrene or marked cellulitis, because of the fact that the afferent lymphatics have become blocked with lymph thrombi that prevent access to the glands of either bacteria or their products.

The inflamed lymph gland is enlarged, swollen, its capsule stretched, and its bloodvessels hyperæmic. Its consistency is at first soft, later more firm, unless suppuration occurs, when it may undergo a partial or complete liquefaction. On section the cut surface is moist, medullary in character, homogeneous, grayish with red mottlings or streaks corresponding to the injected bloodvessels, and from the cut surface an abundant grayish-red or bluish-red tissue juice can be scraped. In severe cases, particularly in the later stages, yellowish or grayish opaque *focal necroses* may be seen throughout the gland substance. As the process becomes older the general color of the affected gland becomes paler, the surface less moist and the consistence firmer, owing to the new formation of lymphocytes and the increase of polymorphonuclear cells, whereby the lymph sinuses become blocked up. The periglandular tissue is also œdematous, hyperæmic, and infiltrated.

On microscopic examination there is seen a lymphoid hyperplasia of the gland, enlargement of the germ centres with numerous mitoses, infiltration of the lymphoid tissue with polymorphonuclear cells, and dilatation of

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the lymph sinuses with a marked desquamation and swelling of the endothelial cells lining the sinus (*sinus catarrh*). Great numbers of lymphocytes and polymorphonuclear cells are found also in the meshes of the reticulum of the sinuses. The efferent lymphatics contain a great excess of cellular elements. In some cases the lymph sinuses may be distended with a fluid exudate poor in cells. Resolution of the inflammatory process may take place at this stage, the cellular exudate may undergo fatty degeneration, the remains of dead cells, disintegrated red cells, blood pigment, etc., may be carried away or digested, and a complete restitution to the normal may occur. In this process the large endothelial cells of the sinuses play a very important part by their phagocytic action. The regeneration of the lymphoid tissue is shown by the great numbers of mitotic figures seen in the pulp and germ centres.

In severe inflammations small areas of degenerating or necrotic cells may occur throughout the affected gland. The nuclei of the cells in these areas may disappear, while the cells themselves become converted into hyaline or granular masses. The exudate in the lymph sinuses may exhibit a *croupous*, *croupous hemorrhagic*, or pure *hemorrhagic* character. The sinuses may become filled with a dense fibrin network, in the meshes of which lie swollen and desquamated endothelial cells, leukocytes, and red blood cells. Active phagocytosis on the part of the desquamated endothelium is usually evident. In other severe forms of lymphadenitis (typhoid fever) the degeneration or the necrosis often becomes very marked, so that a confluence of the focal necroses occurs, and the resulting dead area may take on the appearance of a caseation necrosis. The hemorrhagic and croupous forms occur especially in anthrax, diphtheria, typhoid fever, and bubonic plague. The necrotic form is very common in the mesenteric nodes in typhoid fever. Small focal necroses are also frequently associated with the lymphadenitis of diphtheria.

Lymphadenitis Purulenta.—In certain forms of lymphadenitis, particularly that due to pyogenic infection or to soft chancre, the affected lymph node becomes infiltrated with polynuclear leukocytes, which collect in the areas in which there is a primary degeneration or necrosis of the lymphoid cells caused by the infective agent. Liquefaction of these areas then follows, and abscesses are formed that not infrequently destroy the entire lymph gland and extend into the neighboring tissues (*purulent peri-adenitis*). Suppuration is often long delayed. Fluctuation is usually not obtained until the capsule of the gland has been broken through and the neighboring tissue involved in the suppurative process.

Chronic Lymphadenitis.—Chronic inflammations of the lymph node not caused by any of the specific infections, such as tuberculosis, syphilis, etc., may be due to the presence within the glands of healing abscesses or organizing necrotic foci, to excessive deposits of pigment, dust, etc., in the glands, chronic infections with bacteria of low virulence, absorption of poisons from areas of chronic inflammation in the region tributary to the glands, or from ulcerating or necrotic neoplasms, etc. Even when the neoplasm shows no secondary changes of this kind, the regional lymph glands are practically always in a state of chronic lymphadenitis, due possibly to the absorption of products of tumor metabolism. Chronic irritation of any kind in any given region causes chronic inflammatory changes in the corresponding lymph nodes. As familiar examples, may be mentioned

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the chronic lymphadenitis due to carious teeth, adenoids, slight pharyngeal catarrh, chronic eczema, etc.

Large abscesses or necrotic foci within lymph nodes are gradually replaced by connective tissue as the result of the chronic proliferative inflammation set up about them. The dead tissue is absorbed, granulation tissue takes its place, and with the change of the latter into scar tissue the affected node becomes hard and indurated (*lymphadenitis indurativa* or *proliferans*). The capsule is thickened, the sinuses more or less obliterated, and the lymphoid tissue replaced by fibrous connective tissue. Hyaline degeneration of the latter is very common. In case the dead tissue cannot be absorbed, it is encapsulated by connective tissue, and becomes inspissated or calcified. In the simple forms of chronic lymphadenitis the capsule and stroma are also usually thickened; but there may be a well-marked hyperplasia of the lymphoid tissue, the nodes being very rich in cells without otherwise suffering much structural change. Sooner or later the stroma increases at the expense of the lymphoid tissue, and the gland becomes smaller and indurated. The sinuses may be blocked by proliferating endothelium. Ultimately the glands may become completely fibroid, or may suffer a fatty metaplasia.

Symptoms.—The symptoms in general of lymphadenitis are fever and malaise associated with painful swellings of the lymph nodes. In the purulent form the skin over the enlarged glands becomes red, circumscribed, fluctuation may be recognized, and perforation may finally take place. High fever usually accompanies this form, but in some cases the general symptoms are mild, even when large abscesses are formed. The involvement of deep-lying nodes, between the fascia or muscles, is especially painful. In the general enlargement of the lymph nodes seen in many of the acute infections, so-called glandular fever, etc., of children, all of the lymph glands may be enlargd, hard and shotty, and tender on pressure. In chronic lymphadenitis the only symptoms may be the gradual enlargement of the lymph nodes, usually without pain, although tenderness is often elicited by pressure, and finally the induration. As a result of a chronic perilymphadenitis the lymph nodes may become attached to the skin or surrounding structures and become more or less immovable.

General Lymphadenitis.—A general enlargement of all the lymph nodes of the body associated with fever and general symptoms of intoxication occurs in both children and adults, but is more common in the former. The enlargement is more prominent in the cervical glands, but all of the regional lymph glands may be shotty and tender. Gastric disturbances and either constipation or diarrhœa may form a part of the clinical picture. In many of these cases there is no recognizable local infection, and the general picture is not that of any one of the known infectious diseases. Some of the cases belong to the class grouped under "glandular fever;" while others represent cases of "light measles," rubella, abortive scarlatina, chickenpox, acute pharyngitis, influenza, etc. During influenza epidemics it is not an uncommon thing to see young children in houses containing adult cases develop fever and general glandular swelling without other symptoms. Such forms of general lymphadenitis, as a rule, recover quickly, and suppuration rarely occurs.

A general adenitis may occur in any one of the acute infectious diseases, particularly in young children, and most frequently in scarlet fever, diphtheria, measles, rubella, chickenpox, etc. The condition not infrequently

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terminates in suppuration of some one of the regional groups, most commonly the cervical. Adenoids, chronic tonsillitis, chronic pharyngitis, etc., in young children are also occasionally associated with a universal enlargement of the lymph nodes. A similar chronic condition of the lymph glands is found also in rickets, congenital syphilis, acquired syphilis, lymphatic constitution, etc.

Cervical Lymphadenitis.—This is very common, particularly in children. It may be associated with any form of "sore throat," and may occur as a complication in any one of the acute infections characterized by inflammation of the nose, tonsils, pharynx, larynx, etc. Infection through the gums, lip, face, scalp, alveolar abscesses, carious teeth, irritation of pediculi, eczematous conditions of the face, herpes, furuncles, etc., are among the conditions that may cause or be associated with enlargements of the cervical lymph nodes. In the mild cases the subparotid and the tonsillar lymph nodes alone may be swollen and tender. Suppuration not infrequently occurs in the severe forms of cervical lymphadenitis in children, but cervical abscesses are infrequent in adults, and when occurring are usually found in the submaxillary region and secondary to carious teeth. In young children the abscesses most frequently involve the subparotid nodes and are located beneath the deep cervical fascia and sternocleidomastoid muscle. "Pointing" takes place behind the upper margin of the muscle near the hair line, or anterior to the middle of the muscle on a level with the larynx. The abscesses formed may be of very large size. When under the deep cervical fascia the determination of fluctuation is often very difficult.

"*Ludwig's angina*" may be in some cases a phlegmonous condition involving particularly the lymphatics and lymph nodes of the submaxillary region. The infection usually occurs through carious teeth or alveolar abscesses, and is usually due to the streptococcus. The process may become gangrenous, and is always severe. The prognosis is grave. Usually there is a sudden development of dyspnœa and dysphagia, with severe constitutional symptoms, followed by the formation of a tense phlegmon of the submaxillary region.

Abscesses in the lymph nodes of the *posterior cervical* or *occipital* regions may be caused by infection from furunculosis or pediculosis of the scalp and neck. They are not as severe as those occurring anteriorly, are more superficial and heal more readily.

Retropharyngeal Abscess.—In the majority of cases this condition is due to an infection of the retropharyngeal lymph nodes, following scarlatina, influenza, rhinitis, pharyngitis, tonsillitis, etc. The majority of the cases occur during the first two years of life, since these lymph nodes atrophy after the third year. The abscess usually appears several days after the onset of the acute pharyngitis or rhinitis with which it is associated. Dyspnœa, dysphagia, difficulty in speaking, increase of fever, and general prostration mark the development of the condition. Of these symptoms the dyspnœa becomes the most marked and alarming, particularly in the case of infants. Examination of the posterior pharyngeal wall reveals the presence of a soft fluctuating swelling. This must be differentiated from the non-purulent swelling of the retropharyngeal lymph nodes found in association with large cervical abscesses. When the latter are opened externally, the retropharyngeal swelling disappears promptly. It is also important that the acute retropharyngeal abscesses be distinguished from

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tuberculous abscesses of this region due to tuberculosis of the cervical vertebræ. In the latter case the rigidity of the cervical spine, the character of the general symptoms, etc., will make the differential diagnosis an easy matter. Further, the acute pyogenic infections of the retropharyngeal nodes often give rise in young children to a clinical picture suggesting that of diphtheria, and these cases are not infrequently mistaken for the latter disease. The local examination should settle the question, and there should be no particular difficulty when ordinary care is taken.

Chronic Cervical Lymphadenitis.—A chronic enlargement of the cervical lymph glands, more or less marked, is extremely common in school children. The subparotid nodes are usually affected, and it has been said that nearly all children attending public schools have palpable glands in this region. Such an enlargement is also common in young adults. The constant exposure to cases of infection of the respiratory tract, such a condition being practically everywhere present in our public schools, is probably the chief cause of such chronic enlargements. The relationship between the two conditions is shown by the fact that in the majority of these cases the nodes are palpable or are distinctly enlarged only during the winter months, when respiratory infections are common, and that they subside during the warm season, when such infections are uncommon. Repeated infections in the same individual cause an increase in the size of the glands; and in such cases the nodes may remain permanently enlarged for several years. Interesting questions arise in this connection as to a possible etiological relationship between such chronic enlargements and the condition known as "status lymphaticus." Tuberculosis, Hodgkin's disease, lymphocytoma, and acute leukæmia may apparently develop on the basis of a previous chronic lymphadenitis. Adenoids, enlarged tonsils, otitis, carious teeth, stomatitis, inflammation of the gums, herpes, eczema of face, neck, or scalp, pediculosis, etc., are common causes of chronic cervical lymphadenitis. In some cases the chronic enlargement follows an attack of one of the acute infections, particularly measles and scarlatina.

The question of tuberculosis always arises in these cases of chronic lymphadenitis; and inasmuch as tuberculosis often does develop later in such enlarged nodes, a very careful differential diagnosis should be made. In some cases it is impossible to say whether the nodes are tuberculous from the beginning or whether the infection with tubercle bacilli is secondary to a simple lymphadenitis, the latter condition lowering the resistance of the gland to the tubercle bacilli carried to it. The suspicion of the latter infection should always be entertained in every case of chronic hyperplasia of the lymph nodes, and the prognosis in such cases should be modified accordingly. Since an early diagnosis is of such great importance to the patient, every means should be taken to fix the nature of the process as soon as possible. Calmette's reaction or tuberculin injections may be utilized, the opsonic index taken, or in doubtful cases the removal of one of the enlarged nodes and its careful microscopic examination should be insisted upon. In simple chronic lymphadenitis the microscopic examination shows a simple hyperplasia of the lymphoid tissue alone, or of it and the stroma also. In old cases the lymphoid tissue may become atrophic as the fibroid change increases, and extensive hyaline change may take place.

Lymphadenitis of the Axillary Glands.—Following infected wounds of the hands and arm there may develop a more or less marked inflamma-

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tion of the axillary nodes. As a rule, the majority of those cases run a mild course, and even when large axillary abscesses are produced the general symptoms may be slight. The more serious cases are usually due to the streptococcus; but fortunately they are less common than the milder infections. The lymph nodes should be removed in these severe cases, but in the mild forms with little constitutional involvement the incision of the infected wound and free drainage usually result in a prompt resolution of the axillary swellings. The importance of infected "hang-nails" and cuts on the fingers in the production of ascending lymphangitis of the arm should always be borne in mind in the treatment of these conditions, and should be carefully treated with the view of avoiding such sequelæ. They should not be neglected. Cryptogenic infection of the axillary nodes is not infrequent. Wounds of the fingers or hand received during postmortem examinations or septic surgical operations may sometimes be followed by rapid enlargement of the axillary nodes, with severe general symptoms, occasionally progressing in the course of a few hours to coma and finally death.

Lymphadenitis of the Bronchial Glands.—An acute simple inflammatory enlargement of the bronchial glands occurs in severe forms of bronchitis, pneumonia, and other acute inflammations of the lungs. It is very common in children in association with the acute infectious diseases, particularly when these are complicated with respiratory affections. It is highly probable that in the majority of cases of simple cervical adenitis there is at the same time more or less enlargement of the bronchial nodes. In the ordinary cases the symptoms due to the pressure of the enlarged glands cannot be separated from those of the primary condition; but when the enlargement is marked severe pressure symptoms may be produced. Dysphagia, dyspnœa, respiratory stridor, cyanosis, and the physical signs of bronchial stenosis constitute the clinical picture. Should suppuration occur, the abscess may rupture into the bronchi and sudden death ensue. Chronic inflammation of the bronchial nodes occurs in chronic bronchitis, bronchiectasis, chronic pneumonia, etc.

Lymphadenitis of the Mesenteric Glands.—Simple inflammations are of frequent occurrence in the mesenteric nodes. Severe gastritis, enteritis, peritonitis, appendicitis, omentitis, etc., are among the conditions primary to such enlargements. The enlarged glands are usually discovered at operation, but in some cases, when as large as small hickory-nuts, they may be felt through the abdominal wall, particularly in the appendix region, where they may be mistaken for encapsulated abscesses. Spontaneous resolution of such glands may occur.

Lymphadenitis of the Inguinal and Femoral Glands.—Aside from specific inflammations of the inguinal nodes, simple lymphadenitis is common as a sequel to wounds and inflammatory conditions of the feet or legs. Erysipelas, erythema, eczema, varicose ulcers, gangrene, etc., are some of the many conditions of the lower extremities characterized by swelling of the femoral and inguinal nodes. Infections of the external genitals are also a not infrequent cause of inguinal swellings. Direct trauma is also regarded by some writers as a special cause of inguinal lymphadenitis. After excessive walking, running, jumping, etc., painful swellings of these nodes may appear. Resolution is usually speedy. The so-called *rheumatic bubo* is also found particularly in this region, although the axillary

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nodes may be similarly affected. The rheumatic lymphadenitis is in some cases apparently dependent upon primary rheumatism; in other cases it is traumatic. Chronic inflammations of the lower extremities and external genitals produce chronic lymphadenitis of the inguinal or femoral nodes.

Lymphadenitis in the Acute Infections.—Measles.—In measles there is a more or less well-marked enlargement of all the lymph nodes of the body, particularly those of the posterior cervical, postauricular, and submaxillary groups. In severe cases the enlargement may be very pronounced. Resolution is often delayed, and a distinct chronic hyperplasia may persist. Suppuration is rare, and is usually secondary to some purulent complication of the upper respiratory or auditory tract. An increase in the size of the cervical glands after an attack of measles should always lead to a suspicion of tuberculosis, and appropriate steps should be taken to fix the diagnosis and to institute proper treatment.

Rubella.—This disease is characterized by a marked enlargement of the lymph nodes, usually to a greater extent than in measles. The cervical, submaxillary, postauricular, and occipital nodes may be as large as hickory-nuts, while the remaining regional lymph nodes are distinctly palpable, firm and shotty. The lymphadenitis is usually coincident with the rash, sometimes preceding it by a few days, and gradually disappears. Suppuration is very rare, and the persistence of a chronic hyperplasia much less common than in measles.

Scarlatina.—A more or less pronounced general lymphadenitis is present in practically every case, but often is not noticed. The cervical glands are affected in proportion to the severity of the throat condition. They may be moderately enlarged, hard, and only slightly tender on pressure, or greatly enlarged, soft, and very painful. In the latter case suppuration may occur. Hemorrhages and focal necroses are seen in microscopic examination. This complication may develop early in the disease, or not until all other symptoms have disappeared. As in the case of measles, a tendency to a persistence of the lymphoid hyperplasia is often shown, and the question of a developing tuberculous lymphadenitis is of similar importance in these cases.

Diphtheria.—A lymphadenitis due to the action of the toxin is constantly seen in this disease, and is particularly marked in the severe and fatal cases. Since the cervical glands receive the toxins in the most concentrated form, they show the most marked changes. The enlarged glands are hyperæmic, soft, and homogeneous on section. Hemorrhages and focal necroses occur in the germ centres and also in the lymphoid cords. A fibrin network may be found in the sinuses, follicles, and bloodvessels. The necrotic foci may also contain fibrin threads. In preparations fixed in osmic acid fatty degeneration is seen in the cells of the central portions of the germ centres. A pronounced "sinus catarrh" is usually present, and the endothelial cells show marked phagocytosis. In the severe cases of gangrenous scarlatinal diphtheritis the cervical nodes may present the microscopic picture of a gangrenous or necrotic hemorrhagic lymphadenitis. Chronic hyperplasia of the cervical nodes or of those of the entire body may be seen after diphtheria also, and tuberculosis may develop in such enlarged glands.

Chickenpox.—Slight general enlargement of the lymph nodes is usually present during the onset of this disease; but is usually so slight as not to be noticed unless the nodes are palpated. Chronic hyperplasia occurs more rarely after this affection than in the case of the other infections of childhood.

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Smallpox.—During the onset, the lymph nodes are always more or less swollen, this condition usually increasing until the height of the eruption, when it gradually subsides. On microscopic examination a marked sinus catarrh and œdema of the follicles is found. The structural distinctions may be entirely lost, and the germinal centres may disappear, or changes similar to those found in diphtheria may be present. Great numbers of phagocytes are present in the sinuses. In severe cases hemorrhage may occur or a fibrinous exudate may take place into the sinuses. Focal necroses may occur throughout the lymphoid tissue. Streptococci are often present in the sinuses in large numbers. Usually no reaction occurs; rarely does suppuration take place. The writer has seen a case of generalized streptococcus, suppurative lymphadenitis during convalescence from smallpox.

Vaccinia.—The axillary glands on the side vaccinated are usually enlarged and tender on pressure. Such changes vary greatly in individual cases. They may be wholly unnoticed, or the patient may complain of a feeling of painful tension in the axilla. In cases with marked general reaction all of the regional lymph nodes may be more palpable than normal. Suppurative axillary lymphadenitis may follow secondary infection of the vaccine lesion.

Mumps.—Swelling of the cervical glands is common in severe cases of this disease. The inguinal glands may also be swollen and tender.

Influenza.—A polyadenitis of slight degree is very common in influenza. Swelling of the cervical glands is usually present in proportion to the severity of the throat condition. Children exposed to house epidemics of la grippe may develop moderate fever with general glandular involvement.

Erysipelas.—Lymphadenitis of the lymphatic glands of the region affected often occurs. Suppuration is rare.

Pyæmia and Septicæmia.—A universal enlargement of the lymph nodes is very common. It may be slight or well marked. Pyæmic abscesses may occur.

Acute Rheumatic Fever.—Rarely there is a universal polyadenitis of mild degree. The cervical glands may be tender and swollen when throat complications are present. When pericarditis occurs, the mediastinal glands are usually very much enlarged. Enlargement of the inguinal and axillary nodes may occur.

Anthrax.—The regional lymph glands of the part of the body in which the primary portal of infection is located show a marked hemorrhagic inflammation. Necrosis of the entire gland may result. In such inflamed glands great numbers of bacilli are present.

Glanders.—The lymph nodes are enlarged and show areas of round-cell infiltration. The regional glands of an area in which lymphangitis is present are greatly enlarged and painful. Suppuration may take place. In chronic glanders a chronic hyperplasia of the regional nodes may be seen.

Typhus Fever.—Some enlargement of the lymph nodes may be found in the early stages of this disease.

Typhoid Fever.—A general enlargement of the lymphatic glands is not uncommon in typhoid fever as an expression of the lymphoid reaction to the toxins. It plays no part in the general symptomatology, and is usually unnoticed. Very rarely suppurative lymphadenitis occurs as a late complication or sequel. The streptococcus or staphylococcus is usually found in the abscesses, although the typhoid bacillus may be present.

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Relapsing Fever.—During the onset of the attack an enlargement of the lymph nodes may be noted in association with the rapid increase in size of the spleen.

Epidemic Cerebrospinal Meningitis.—The glands may be slightly enlarged, soft, and hyperæmic.

Pneumococcus Septicæmia.—A general enlargement of the lymph nodes is usually present in this condition. Local infections due to the pneumococcus cause more or less regional lymphadenitis.

Infectious Jaundice.—Slight general lymphadenitis may be present.

Miliary Fever.—Slight general lymphadenitis.

Rocky Mountain Spotted Fever.—A more or less pronounced general enlargement of the lymph nodes.

Foot and Mouth Disease.—The submaxillary lymph nodes are usually enlarged and painful.

Glandular Fever.—This disease is characterized by a lymphadenitis of the cervical group usually, but sometimes of the axillary, inguinal, mediastinal, or mesenteric glands.

Malta Fever.—Slight enlargement of the mesenteric glands occurs.

Amœbic Dysentery.—The lymph nodes of the mesocolon are often enlarged, hyperæmic, and œdematous. On microscopic examination they show a "sinus catarrh." Focal necroses and hemorrhages are rare.

Bacillary Dysentery.—The lymphoid tissue of the intestine, the mesenteric and retroperitoneal glands is hyperplastic and often hemorrhagic. The nodes may contain focal necroses. Great numbers of bacilli may be found in the glands.

Malaria.—Swelling and pigmentation of the lymph nodes occurs in pernicious malaria. In chronic malaria the nodes may show the picture of a chronic lymphadenitis.

Trypanosomiasis.—A chronic polyadenitis is a constant feature of human trypanosomiasis, both the superficial and deep glands being involved, the latter usually to a greater degree. On microscopic examination the enlarged nodes show proliferation of the lymphoid tissue and stroma, hemorrhage, marked pigmentation, necrosis, etc. In the later stages the lymphoid tissue may be greatly reduced, the greater part of the gland consisting of newly formed, connective tissue. The lymph nodes may contain a greater amount of blood pigment than the spleen. Great numbers of phagocytes may be found in the sinuses and throughout the lymphoid tissues. Secondary pyogenic infection sometimes occurs and abscesses are formed in the enlarged nodes. Trypanosomes apparently occur in greater numbers in the enlarged lymph glands than in the blood or the cerebrospinal fluid. Advantage of this fact has been taken in the diagnosis of the disease. A drop of fluid aspirated from an enlarged cervical gland and properly examined reveals at once the presence of the parasites.

Bubo.—This term is sometimes used in a loose way to designate any marked inflammatory enlargement of a regional group of lymph nodes, but is more commonly and properly applied to the swellings of the inguinal and femoral nodes occurring particularly in the venereal infections and in plague. It is also used to designate non-venereal inflammations of these glands resulting from infected wounds of the lower extremities of external genitals. The term is also applied to the glandular lesions of bubonic plague occurring in any region of the body. Inflammatory enlargements

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of the inguinal and femoral nodes following excessive exercise or associated with rheumatism are known as "traumatic bubo" and "rheumatic bubo."

Gonorrhœal Bubo.—Inflammatory enlargements of the inguinal nodes due to gonorrhœa are more common in the male, although not infrequent in the female. In the latter an associated lymphangitis is also less common. The affected glands are painful and swollen, and these symptoms may persist for some time without change, resolution then occurring. The enlargement is usually moderate. Occasionally, particularly in cachectic individuals or as the result of other influences, such as excessive exercise, trauma, etc., a secondary pyogenic infection takes place and suppuration occurs, and the course of the condition may be protracted. It is also probable that the gonococci alone may produce a suppurative lymphadenitis. In the non-suppurative gonococcal bubo the microscopic examination shows the presence of a simple lymphadenitis, with polymorphonuclear infiltration, "sinus catarrh," etc. Gonococci may be found in polynuclear cells in the lymph sinuses. The microscopic picture of the suppurative form possesses nothing distinctive from that due to other pyogenic infections.

In general the course and symptoms of gonorrhœal bubo resemble those of the bubo of soft chancre. The entire chain of glands from the anterior superior spine to the symphysis may be enlarged and the surrounding tissues so infiltrated that the individual nodes cannot be made out. In cachectic individuals the condition may be severe and protracted; in the majority of cases it runs a relatively mild course.

Chancroid.—Bubo is an extremely common complication of soft chancre, particularly in the male. It may develop at any time during the course of the soft chancre, or even after the latter has healed. When the lesion is located upon the genitals the inguinal nodes are affected; when located in other parts of the body the corresponding regional nodes are involved. The afferent lymphatics may or may not be the seat of an ascending lymphangitis. Very often the nodes are involved without any signs of inflammation of the lymph vessels. The lymphadenitis develops acutely with severe pain, and often chills and fever, the affected glands frequently reaching the size of a small orange. There is considerable peri-adenitis, so that the entire group of nodes may appear as one solid mass. The swelling may occur on one side or on both. Usually the side affected corresponds to the seat of the lesion, but not infrequently the bubo may develop on the opposite side. The skin over the bubo is usually reddened and œdematous. The pain may be so severe as to interfere with the use of the legs. Within two or three weeks from the development of the bubo fluctuation may be felt and perforation through the skin usually follows. Resolution without suppuration is rare and takes place only in buboes of small size. With the advent of suppuration the pain usually diminishes in intensity, and may cease entirely with the rupture of the abscess. Repeated abscess formation may take place, or the entire chain may be converted into one large abscess. The latter event may often be prevented by early incision. Occasionally septicæmia develops, leading to a fatal issue. Some buboes due to soft chancre run a very malignant course; destructive serpiginous ulcers may be formed, or the process may assume the character of a spreading gangrene. In the majority of cases healing occurs after a more or less chronic course. Metastasis from the lymph nodes has not yet been observed, and is usually stated never to occur. The microscopic examination shows a suppurative lymphadenitis

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with necrosis and hemorrhage. While recovery is often very slow, the prognosis in general is good.

Syphilis.—The bubo of syphilis develops usually about four to five weeks after infection. The swelling of the inguinal glands is less acute, of slow development, and less painful than in the case of soft chancre. The glands alone are involved, the periglandular tissue usually remaining free. The enlarged nodes are rarely larger than a cherry; usually the entire chain of nodes is involved (syphilitic rosary). Both sides are usually affected, the nodes on the side on which the primary sore is situated being the larger. In uncomplicated cases suppuration does not occur, but in the case of mixed chancre an acute suppurative lymphadenitis may develop. The course of the pure syphilitic bubo is a very protracted one (*"indolent bubo"*). Since the symptoms are slight, the patient pays but little attention to the condition. On microscopic examination the syphilitic bubo shows a lymphoid and endothelial proliferation, blocking of the sinuses with new endothelial cells and fibroblasts, loss of structural characteristics, and in the later stages a fibroid change. Spirochætæ may be demonstrated in the hyperplastic nodes. Both afferent and efferent lymphatics show endothelial proliferation and obliteration of the lumen from the thickening of their walls. Collections of lymphocytes and plasma cells are found about the lymphatics and also the bloodvessels. Similar changes occur in the regional nodes of any part of the body in which the primary sore may be located. Resolution of the syphilitic bubo is attended by a fatty degeneration of the newly formed cellular elements. Atrophy and fibroid change usually follow.

Bubonic Plague.—The lymphatic nodes are specially involved in this disease, and the changes occurring in them form the chief features of the infection. The development of the bacillus apparently takes place more rapidly in the lymph nodes than elsewhere in the body. Periglandular œdema, infiltration, hemorrhagic necrosis of the lymphoid tissue and suppuration are the chief pathological features. Primary, secondary, and tertiary buboes are the clinical features of the lymph-node condition. (See p. 763, Vol. II).

Treatment of Lymphadenitis.—The general indications in simple lymphadenitis are the removal of the infective agent, the prevention of suppuration, and the restoration of the glands to their normal condition. When suppuration has occurred the removal of the pus and the free drainage of the abscess are the chief therapeutic measures. The general condition of the patient demands special consideration. Careful attention must be paid to nutrition, general hygiene, etc. Rest of the affected region may be obtained by the use of splints, "pasteboard stocks," etc.

The proper management of the local infection usually brings about a prompt resolution of the lymphadenitis. In the cervical region the proper treatment of tonsillitis, pharyngitis, rhinitis, stomatitis, otitis, carious teeth, alveolar abscesses, furuncles, eczema, herpes, pediculi, etc., is the chief indication in those cases of lymphadenitis due to any one of these causes. Local treatment in the form of ice-bags, cold compresses, etc., is usually employed in an effort to increase the patient's comfort. Under such simple measures the adenitis associated with the acute infections usually disappears promptly in a large percentage of cases; and, in fact, such a resolution often occurs when no local treatment is given to the inflamed nodes. The use of iron, arsenic, and the iodides is still advocated as a therapeutic measure

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intended to raise the general strength and resisting power of the patient. All hygienic measures having this aim should be employed according to the indications of the given case. Fresh air and proper feeding are more important than the administration of such drugs.

In the treatment of chronic lymphadenitis various external applications, such as lead acetate, potassium iodide, lead iodide ointment, tincture of iodine, etc., are used locally to aid in resolution. The role played by these applications is a doubtful one, and they are to a certain extent falling out of use. Should they be employed, excessive irritation of the skin should be carefully avoided.

In the treatment of bubo before suppuration has occurred, local applications of the tincture of iodine and belladonna, iodide of lead, lead acetate, etc., are much used in the form of moist dressings, ointments, plasters, etc. Injections into the bubo of benzoate of mercury, carbolic acid, mercuric chloride, silver nitrate, etc., are also advised, but the present tendency is toward less radical treatment. Rest in bed with warm applications, moist alcohol dressings covered tightly with rubber tissue or oiled silk, pressure bandages, etc., constitute the chief measures of treatment before suppuration takes place. Cauterization of the primary sore is regarded by some writers as favoring the development of bubo, the superficial crust formed increasing the growth of the infective agent and thus promoting the chances for involvement of the lymphatics and metastasis to the inguinal glands. After suppuration the treatment is surgical.

The treatment of the various forms of acute lymphadenitis due to specific agents, as the glanders bacillus, plague bacillus, anthrax, etc., will be found in the sections treating of these diseases.

Tuberculosis.—This is, next to lymphadenitis, the most common affection of the lymph nodes. The peribronchial, mesenteric, and cervical groups are most frequently affected. The infection may be either hæmatogenous or lymphogenous, the latter being much the more common. In the majority of cases the tuberculous lesions in the lymph nodes are secondary to a primary focus in the region tributary to them; more rarely a primary cryptogenic infection of a node may occur. Three pathological varieties exist.

1. Miliary tubercles occur, either single or multiple. In the early stages they may be either *lymphoid* or *epithelioid*, usually the latter. Giant cells may or may not be present. Caseation occurs sooner or later. As the tubercles increase in size and number they may become confluent and gradually form large caseous masses. There is always an associated simple adenitis and peri-adenitis. Secondary infection and suppuration of the caseous areas often take place. Cyst-like spaces may thus be formed in the node, and perforation into a bronchus, the pleural or pericardial cavity, bloodvessel, lymph vessel, or through the skin may occur. A fistulous tract or an ulcer the sides of which are composed of tuberculous granulations may be thus formed. Streptococci are usually found in the pus. In other cases, after the death of the bacilli the caseous areas become inspissated or calcified, a dense connective-tissue capsule being formed about the mass. Secondary liquefaction of the caseous material leads to the formation of a cyst. A portion of a node may alone be involved, or the entire node may be so changed.

2. The affected node may present a *diffuse cellular hyperplasia*, either

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lymphoid or epithelioid in character, according to the age of the process. Giant cells may or may not be present. Caseation may be entirely absent. The lymphoid tissue may become wholly replaced by epithelioid tissue, usually somewhat nodularly arranged, as if developing through the confluence of many foci. Few bacilli can be demonstrated on staining. The whole picture suggests an infection of low virulence. The affected nodes slowly enlarge, remain stationary sometimes for years, and gradually become hard and indurated. Contraction then follows. On section they may appear homogeneous, smooth, semi-translucent, and grayish or brownish in color. The development of connective tissue around the nodular centres of epithelioid proliferation often gives a granular appearance to the cut surface. The centres of the epithelioid foci may show a slight caseation. The cervical, axillary, cubital, and inguinal glands most frequently show this form of tuberculosis. Rarely all of the lymph nodes of the body may present such changes, the clinical picture being that of Hodgkin's disease.

3. The third form is characterized by a rapid caseation and softening, beginning either in one focus or in a number of foci scattered through the node. A node may quickly be completely caseated. On section the surface is smooth, dry, homogeneous, yellowish in color, and crumbling to the touch. Tubercle bacilli are present in large numbers, and the process is virulent in character. Epithelioid and giant cells may not be formed, and there may be no true tubercle formation, the caseation representing the primary destruction of the lymph node. The cervical, mesenteric, and bronchial nodes most frequently show this form of tuberculosis, and it is usually seen in children or cachectic individuals with low resistance. Secondary infection and suppuration may follow.

Combinations of two of these forms or of all three occur. There is no hard-and-fast line between them, nevertheless they occur sufficiently well-defined to constitute both clinical and pathological entities. Particularly is this the case with the diffuse cellular hyperplasia, the clinical picture being that of Hodgkin's disease or generalized lymphocytoma. The slowly caseating form (chronic tuberculous lymphadenitis) and the more rapid virulent form (acute tuberculous lymphadenitis) also constitute well-marked clinical entities.

Tubercle bacilli are constantly received by the lymph nodes and destroyed by them, in the great majority of cases without the production of any perceptible lesion. It is, of course, well known that positive results may be obtained by the inoculation of lymph nodes showing no tuberculous changes. In other cases minute focal necroses may be formed before the bacilli are killed off or are inhibited in their growth. The spontaneous healing of small tubercles is also of frequent occurrence. The site of such healed lesions is usually shown by the formation of a hyaline mass. It is the writer's belief that the small hyaline areas so common in lymph nodes, particularly in those of the mesenteric and retroperitoneal regions, represent in the majority, if not in all cases, small healed tuberculous lesions.

The presence in the body of lesions containing virulent tubercle bacilli is a constant menace to the safety of the organism. Rupture of the caseous area into a lymph vessel, thoracic duct, or vein may give rise to a generalized miliary tuberculosis. Likewise, the occurrence of tuberculous meningitis as a sequel to tuberculous lymphadenitis is not uncommon. In cases of tuberculosis of the bronchial glands occurring in children a simple broncho-

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pneumonia due to measles or scarlatina may become converted into a widespread caseous pneumonia. The possibilities of such sequelæ make tuberculosis of the lymph nodes a very grave affection, particularly in children.

The cervical, bronchial, and mesenteric lymph nodes are most often the seat of tuberculosis. In the case of the *cervical glands* the submaxillary nodes are more frequently involved. The infection may reach the glands through the mucosa of the upper respiratory tract without the occurrence of local lesions; or the tuberculous lymphadenitis may be secondary to a tuberculosis of the tonsils, adenoids, nose, pharynx, middle ear, skin, etc. Carious teeth may form an avenue of entrance for the bacilli. The nodes may enlarge slowly or an acute enlargement may take place. Single nodes may be involved, or the entire group may show evidences of infection. A nodular mass may be formed along the jugular vein. For months or even for several years the condition may show no change, although there is usually a tendency toward a progressive involvement of a number of nodes. Suppuration and perforation of the skin occur very frequently. The affection is most common during childhood and youth, and in individuals living under bad hygienic conditions. Infants are rarely affected. The majority of the patients appear for treatment during the latter part of the winter and early spring.

Tuberculosis of the *bronchial nodes* may be primary, the bacilli either passing the lungs without exciting lesions there, or they are brought to the nodes through the thoracic duct. Secondary involvement occurs in tuberculosis of the lungs, cervical nodes, vertebræ, ribs, sternum, clavicle, mammary gland, etc. Some writers hold that the entrance of tubercle bacilli intc the lymph in any part of the body may cause tuberculosis of the bronchial nodes. Bacilli taken through the intestinal mucosa without producing any lesion in it may be carried through the thoracic duct and through the lungs to excite first in the bronchial nodes the characteristic lesions of tuberculosis. The affected nodes may be large or small, hard or soft, indurated or calcified. Large caseous masses may be formed. Pressure upon the trachea or bronchi may give rise to a respiratory stridor; while compression of the heart or great vessels may cause circulatory disturbances. Dyspnœa, stridor, asthma-like attacks, hoarseness, cough, cyanosis, dysphagia, vomiting, paralysis of vocal cords, inequality of pupils, etc., are the chief clinical symptoms. The sternum may be arched forward. Severe pain is often felt in the region of the upper dorsal vertebræ. An area of dulness may be obtained by percussion, and the *x*-ray picture may show definite shadows corresponding to the diseased nodes. Loud venous murmurs may be heard on auscultation. These are probably due to the pressure upon the left innominate vein. Perforation may take place into the bronchi, lungs, pleura, pericardium, trachea, œsophagus, or large vessels. Aspiration tuberculosis, usually in the form of a caseous pneumonia, may be produced in the lungs, or a general miliary tuberculosis or tuberculous meningitis may form the final phase of these cases.

Infection of the *mesenteric nodes* may take place from bacilli that pass the intestinal mucosa without exciting any lesion there; or it may be secondary to tuberculous lesions of the intestine or of any part of the body tributary to the thoracic duct. The bacilli may be either the bovine or the human strain. The former is found chiefly in infants as the result of the ingestion of milk from tuberculous cows. Infection with the human strain

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is usually the result of auto-infection of the intestine from bacilli swallowed in the sputum. Bacilli taken in with dust and swallowed with the saliva may also give rise to mesenteric tuberculosis. In the opinion of the writer healed tuberculosis of the mesenteric and retroperitoneal nodes is of very frequent occurrence. In the great majority of adult cadavers small hyaline areas may be found in these nodes. An extensive study of these has led the writer to believe that the majority, if not all, of such hyaline deposits represent healed tuberculous lesions. The entrance of tubercle bacilli into the mesenteric and retroperitoneal nodes must then be of very frequent occurrence, and the importance of the intestinal route of infection must be emphasized. The early healing of such lesions indicates an infection with a strain of low virulence, possibly the bovine form. As a distinct clinical entity, tuberculosis of the mesenteric nodes is not nearly so common as that of the cervical nodes. It occurs as such chiefly in children under the clinical picture of *tabes mesenterica*. In this affection the mesenteric nodes may become converted into large nodular caseous masses. Absorption from the intestine is greatly diminished. The child becomes greatly emaciated, the abdomen is distended, and an insatiable appetite, diarrhœa, and offensive stools are the chief symptoms. A fatal termination is inevitable. Only rarely does tuberculosis of the mesenteric nodes occur in such a localized form that surgical removal is possible. Since the condition is usually associated clinically with tuberculosis of the intestines, peritoneum, or other part of the body, surgical interference does not offer promising results.

Tuberculosis of the *axillary nodes* is not rare, and is usually associated with tuberculosis of the arm or mammary gland. Tuberculous warts received through autopsy or surgical operation may be the source of the bacilli carried to the lymph nodes. The *epitrochlear gland* is usually involved also, or may alone be affected.

The *inguinal nodes* are also not infrequently the seat of a tuberculous infection. Tuberculous ulcers of the foot following wounds are the most common sources of the infection, but it may be associated with tuberculosis of the external genitals. The involvement of the lymph nodes may be rapid or slow, and the course virulent or very mild.

Generalized tuberculous lymphadenitis is relatively rare. The condition is very chronic, slowly progressive, and presents a clinical picture that often cannot be differentiated from that of Hodgkin's disease except by a microscopic examination of one of the affected nodes removed for this purpose. The writer has seen several cases, all diagnosed as Hodgkin's disease, and in every way showing the clinical characteristics of the latter affection; but the microscopic examination of excised nodes showed the presence of a diffuse, non-caseating epithelioid tuberculosis with few giant cells. In one case under the tuberculin treatment the nodes increased in size, and a second examination showed beginning caseation and a greater number of giant cells. The microscopic features of such a form of tuberculosis are wholly distinct from those of true Hodgkin's disease.

Differential Diagnosis.—The diagnosis of a tuberculous lymphadenitis is often very difficult or wholly impossible without a microscopic examination. In the early stages it is very difficult to distinguish between simple hyperplastic lymphadenitis and tuberculosis. Persistence for several months of the glandular enlargement, a swelling of the gland to the size of a hickory-nut, a beginning softening, etc., are the chief indications of tuberculosis.

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Since it is important that the diagnosis should be made early, the excision of a node for microscopic examination should be insisted upon. This can be done without danger, and should leave no perceptible scar. The microscope often shows that nodes removed from the neck as tuberculous present an entirely different process—simple inflammation, neoplasm, dermoid cyst, Hodgkin's disease, lymphocytoma, etc. In the case of the enlargement of the nodes of a given region or of the entire body, the differential diagnosis will depend upon the microscopic examination of an excised node. This becomes the final resort. The clinical differentiation usually given cannot be depended upon. Calmette's reaction or the tuberculin test may also be used in doubtful cases.

Treatment.—The general treatment for tuberculous lymphadenitis is that for tuberculosis in any part of the body. Rest, fresh air, and abundant and proper feeding are the chief means of increasing the patient's general resistance. Under such hygienic measures some patients greatly improve, and healing of the tuberculous process may take place. The internal use of potassium iodide, iron, and arsenic is still regarded by some practitioners as of great value. Counterirritation, injections of iodine, mercury, carbolic acid, etc., incision and drainage, etc., are still used in the treatment of softened nodes. By the best representatives of the modern school such methods are regarded as bad, and but one thing is advised—the early removal of the affected nodes. All cases, therefore, should be regarded as surgical as soon as the suspicion of tuberculous lymphadenitis becomes well founded. The operation is a perfectly safe one in good hands, and the results in many cases are perfect. To a large extent these depend upon the thoroughness of the operation. A large incision should be made, and the entire group containing the affected nodes should be cleaned out. It is unwise to remove only those nodes that are apparently enlarged. The mistake is often made by the general practitioner of making a small incision and removing only one or two enlarged nodes. Recurrence practically always takes place after such incomplete operations. It is best, therefore, to turn the case over to an experienced surgeon. The proximity of the nodes underneath the sternocleidomastoid to the spinal accessory nerve and internal jugular vein make their removal a matter of careful work. The scar resulting from a good operation is very slight, and is not to be compared with the disfigurement resulting from spontaneous perforation. The latter event should never be allowed to occur. After the operation the patient should be treated for some time along antituberculosis lines.

The use of the Röntgen rays is not advised for the treatment of tuberculous lymph nodes. Too many dangers attend the prolonged and vigorous irradiation necessary to reduce the size of enlarged nodes. Moreover, in glands so treated an active eruption of miliary tubercles may occur at the periphery of the caseous areas. Tuberculin, the vaccine method, etc., may be also employed. In the rare cases of general tuberculous lymphadenitis these are about the only therapeutic measures offering any hope of delaying the course of the disease. Surgical removal of all the regional lymph nodes is not possible, but the groups showing the greatest involvement may be removed and specific antituberculosis treatment carried out.

Scrofula.—Modern medicine does not recognize a distinct clinical entity under the term "scrofula" or "scrofulous." The clinical complex of chronic hyperplasia of the cervical, bronchial, and mesenteric lymph nodes, leading

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sooner or later to caseation, associated with tuberculous processes in the bones and joints, chronic inflammations of the mucous membranes of the eyes, ears, nose, pharynx, swollen lips, "scrofulous habitus," etc., is regarded only as a special form of tuberculosis peculiar to children.

Syphilis.—Aside from the bubo attending the primary lesion, constitutional syphilis is associated with two distinct forms of changes in the lymph nodes, cellular hyperplasia, and gumma. In the first the nodes are moderately enlarged, hard, homogeneous, and grayish on section. The glands in any part of the body may be affected, particularly the inguinal, cervical, occipital, pectoral, and cubital nodes. These may become affected early in the secondary stage, and the enlargement may persist for many years, the nodes finally becoming atrophic and indurated. On microscopic examination, hyperplasia of the lymphoid cells, reticulum, and sinus endothelium, with infiltration of the vessel walls, etc., is found. In the later stages the lymphoid tissue becomes atrophic and the nodes may come to consist wholly or chiefly of dense, hyaline, connective tissue. Gummata are found but rarely in the lymph nodes, and are practically always located in the regional lymph nodes of an organ containing gummata. In cases of gummata of the liver the nodes at the portal fissure may contain gummata, while in gummata of the skin or muscles the corresponding nodes may be similarly affected. Suppuration is less common in syphilitic nodes than in tuberculous, but abscesses are sometimes formed. The diagnosis is usually easy from the history and associated lesions. In cases of doubt a node may be removed for microscopic examination, and this should be done in all cases in which the diagnosis is not clear. The treatment is along antisyphilitic lines.

Leprosy.—In leprosy the lymph nodes of an affected region or throughout the entire body may be enlarged, firm, and yellowish white on section. Microscopically, a condition of cellular hyperplasia is present and leprabacilli may be demonstrated in the lymphoid tissue.

Retrograde Changes.—Simple atrophy, with or without *fatty infiltration*, occurs in old age and in general obesity, anæmia, cachexia, etc. The node may be completely changed into a kidney-shaped fat lobule having a thick capsule; or fat cells may occur in numbers throughout the lymphoid tissue. *Fatty degeneration* occurs in the lymphoid cells after Röntgen irradiation, resolution of glandular hyperplasias, buboes, etc. *Amyloid* may occur in association with general amyloidosis, or as a local change following syphilitic inflammation, etc. It is found also in lymphomata, indurated nodes of Hodgkin's disease, etc. *Hyaline degeneration* is very common in chronic lymphadenitis, tuberculosis, secondary carcinoma, Hodgkin's disease, etc. The great majority of the localized hyaline areas in lymph nodes represent, in the writer's opinion, healed tuberculous lesions. This is particularly true of the small hyaline areas in the mesenteric and retroperitoneal nodes. *Calcification* is very common in old tuberculous lesions, necrotic areas, hyaline deposits, old abscesses, secondary tumors, etc. True *bone* may be formed in old calcified tubercles. *Caseous necrosis* of the lymphoid tissue may be produced by Röntgen irradiation, action of many pathogenic bacteria, etc.

Pigmentation of the lymph nodes occurs through deposits of carbon dust (anthracosis), blood pigment (hæmosiderosis), pigments used in tattoo, bile pigment (icterus), and melanin (Addison's disease, melanotic sarcoma, etc.). The nodes may be enlarged, hard, and indurated, or soft and friable.

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Fatty degeneration and caseation or liquefaction necrosis may occur when the amount of pigment is large. Rupture of a softened node into the blood stream leads to a general metastasis of the pigment. In the great majority of cases such perforations are due to an associated tuberculosis of the pigmented node. Miliary tuberculosis often follows such a pigment metastasis.

Secondary Neoplasms.—Secondary *sarcoma* occurs frequently in the lymph nodes, metastases even of the harder forms, such as osteosarcoma, not infrequently being found in the regional nodes. In the case of softer and more malignant forms, such as round-cell melanotic sarcomata, the regional nodes usually become involved very early. *Endotheliomata*, particularly those of the serous membranes, may also give rise to secondaries in the lymph nodes. *Secondary carcinoma* occurs in the lymph nodes with much greater frequency than secondary sarcoma. In all of its various forms carcinoma shows a special tendency to invade the lymphatics and give rise to metastases in the regional nodes. Usually the secondary growth has a structure like that of the primary, but it sometimes shows a very different one. The young metastases are richer in cells, soft, and possess relatively little stroma. For this reason the malignant nature of a scirrhus carcinoma can usually be best made out in the metastases found in the lymph nodes, the primary growth often, both to the naked eye and microscopically, apparently consisting of an inflammatory new formation of connective tissue.

The symptoms of the secondary development of tumors in lymph nodes are the progressive enlargement of the regional nodes, periglandular infiltration, secondary degeneration, lymph stasis, etc. It must be remembered, however, that nodes apparently not enlarged may have their elements wholly replaced by tumor tissue. In other cases the metastatic growth may exceed the primary in size. The consistence may be hard or soft; the cut surface is usually whitish, sometimes mottled. On scraping, an abundant cell juice can be obtained from cellular tumors. The differential diagnosis rests wholly upon the microscopic findings. The regional lymph nodes of any organ the seat of a malignant neoplasm practically always show a chronic lymphadenitis, and an enlargement of the nodes may be due to this when no metastases are present, but a positive diagnosis can be obtained only through microscopic examination. The treatment of metastatic tumors of the lymph nodes is wholly surgical. In inoperable cases Röntgen irradiation may be used to check the growth and prevent further metastases.

Secondary Leukæmic Changes.—The lymph nodes may be involved secondarily in either lymphæmia or myelæmia of bone-marrow origin. In chloroma, likewise, the nodes show secondary changes. The enlargement may be slight, or large nodular tumors may be produced in the regional groups. Röntgen irradiation and the administration of arsenic constitute our only effectual therapeutic measures.

PRIMARY AFFECTIONS OF THE LYMPH NODES.

These consist almost wholly of progressive hyperplasias and tumor-like formations, the etiology and nature of which is not clear. They practically all run a malignant course, leading sooner or later to death. Compared with the secondary affections of the lymph nodes they are relatively rare, but

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are by no means infrequent. In the literature they appear under a great variety of designations, and a satisfactory classification of the reported cases is impossible. According to the writer's belief, based upon an unusually large pathological material of this kind, the majority of the conditions are genetically related and show transition phases. This is particularly true of the leukæmic and aleukæmic lymphocytomata (lymphomata, lymphosarcomata).

Lymphocytoma.—The hyperplastic and neoplasm-like conditions of the lymph nodes depending upon an overgrowth of cells of the type of lymphocytes, either of the small variety or the large, are here brought into one general class, the *lymphocytomata*. This includes all the lymphocytomatous tumors classed variously as lymphoma, lymphadenoma, lymphosarcoma, pseudoleukæmia, adenia, lymphadenomatosis, lymphomatosis, etc. In all of these conditions the essential thing is an *overgrowth of lymphocytes* occurring primarily in preëxisting lymphoid tissue. All stages of transition exist between glands in which there is a simple lymphoid hyperplasia and tumors the cells of which infiltrate the capsules of the nodes and invade the neighboring tissues. The former are usually classed as benign lymphoma, lymphadenoma, pseudoleukæmia, etc., while the more malignant infiltrating varieties are grouped under the head of lymphosarcoma. In all cases cells of the lymphocyte type constitute the essential tumor element, and for that reason all the forms, including all the transition varieties between one extreme and the other, may be conveniently grouped under the head of lymphocytoma. From the ordinary forms of sarcoma the lymphocytomata are distinguished by the fact that the latter spread progressively through the lymphatic system and do not set up hæmatogenous metastases. The writer believes that all of these lymphoid hyperplasias are genetically related. They may be divided into two great groups, *leukæmic* and *aleukæmic*, according to the blood condition. So far as the essential pathology is concerned, no histological difference can be discovered between these two types, and one may pass into the other. A further classification is that of *generalized* and *localized* or *regional lymphocytoma*. According to the slowness or rapidity of the course a clinical classification into *benign* or *malignant* lymphocytoma may also be made, but it must be borne in mind that in all cases the process is a progressive one, although the course at times may be very slow.

Generalized Aleukæmic Lymphocytoma.—All of the lymph nodes may at the same time or in succession show a progressive enlargement. Large nodular masses may be formed in the cervical, axillary, etc., regions The individual nodes may be felt, or they may be fused together. The consistence may be firm or soft. Fluctuation may occur. The nodes may or may not be adherent to the overlying skin. Spontaneous resolution of enlarged nodes may occur at times. The general condition may remain good, or fever, tendency to hemorrhage, inflammations, etc., may develop. In some cases the patients rapidly become emaciated and quickly die. Pressure from the enlarged nodes may cause œdema, ascites, chylous ascites, chylothorax, compression of the trachea, suffocation, etc. Cases that have run a benign course for many years may suddenly become malignant in character or may develop leukæmia. In the malignant forms the tissue about the nodes becomes infiltrated, the liver, lungs, kidneys, bone-marrow, and all the serous surfaces may show infiltrations or nodular metastases. In the

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so-called benign forms similar infiltrations and lymphomata are found in the internal organs, particularly in the liver. The growth of the tumors may be very rapid, and extensive areas of degeneration and necrosis may be found in them. Perforation and ulceration may occur. Microscopically the rapidly growing forms show a more atypical structure than the benign forms. According to the development of the stroma *hard* and *soft* forms may be produced.

Regional Lymphocytoma.—This form differs from the above only in the fact that the tumor-like growths develop in certain regions, while the other lymph nodes of the body show a much less degree of involvement, often being only moderately enlarged. The course of the disease is a progressive one, and aside from the changes due to the local tumors, the pathological picture is essentially the same as that seen in the generalized form. The following varieties may be distinguished:

1. Symmetrical enlargement of lacrimal or salivary glands. Failure of lacrimation and xerostomia are the special symptoms dependent upon the local enlargements. (See Plate XIII, Fig. 1.)
2. Mediastinal lymphocytoma with pressure symptoms as the most important clinical features.
3. Lymphocytoma of stomach or intestine and mesenteric glands. The chief symptoms are abdominal tumor, achylia, diarrhœa, ascites (chylous), chylothorax, œdema of lower extremities, etc. In the writer's experience this has been one of the most common forms. Four cases of this type have occurred in his pathological material of the last two years. (See Plate XIII, Fig. 2, and Plate XIV.)
4. Retroperitoneal lymphocytoma, with symptoms similar to preceding.
5. Cervical or axillary lymphocytoma, often unilateral.
6. Lymphocytoma of the pharynx.
7. Lymphocytoma of the skin (mycosis fungoides).

These are the most common and striking clinical varieties, but any region (rectum, testicles, etc.) may be the seat of the chief growth. The remaining lymph nodes may show a moderate enlargement, miliary lymphoid nodules may be found in the lungs, liver, kidneys, spleen, adrenals, parotid, bone-marrow, omentum, etc., while the spleen, as a rule, is not greatly enlarged or not at all. The writer has seen lymphatic leukæmia develop in three cases of the intestinal type, in two cases of symmetrical enlargement of the lacrimal glands, and in one case of pharyngeal and cervical localization.

Diagnosis.—The diagnosis rests chiefly upon the microscopic examination of one of the enlarged nodes, excised for this purpose. Much time will be saved if this procedure is carried out early.

Treatment.—Both the *generalized* and the *regional* forms of lymphocytoma are incurable. The benign forms run a slow course, often into old age, while the duration of the malignant type is usually two to three years. Cases running a benign course at first may later take on a malignant character. The internal use of arsenic and the careful use of Röntgen irradiation may serve to delay the fatal termination. Although the tumors may be greatly reduced by such treatment, symptoms of intoxication may arise and the patient die while it is being carried out. The surgical treatment may give prolonged relief in the case of the slowly growing forms, but operation is always followed by recurrence in the case of the more malignant type and often in the benign. No matter how thoroughly a region may be freed of

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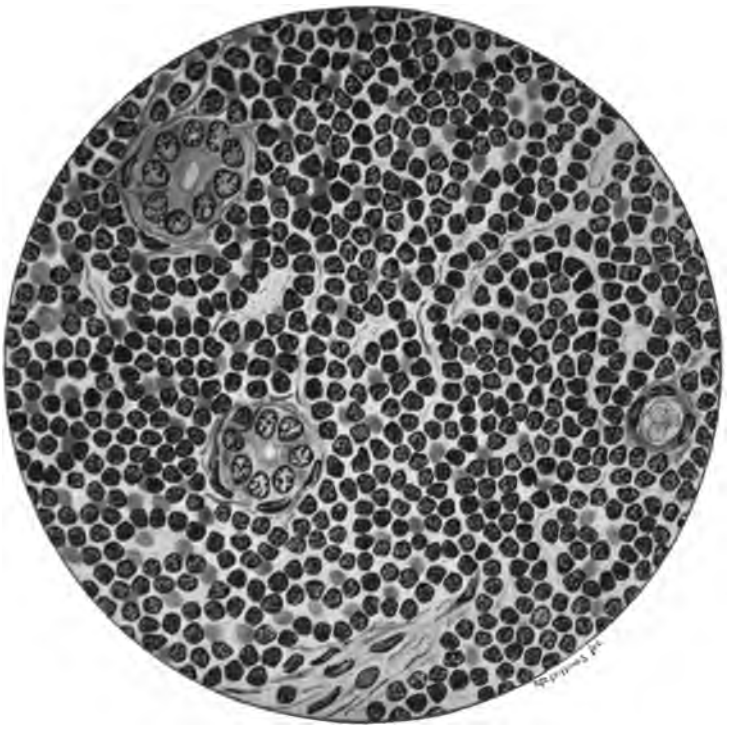
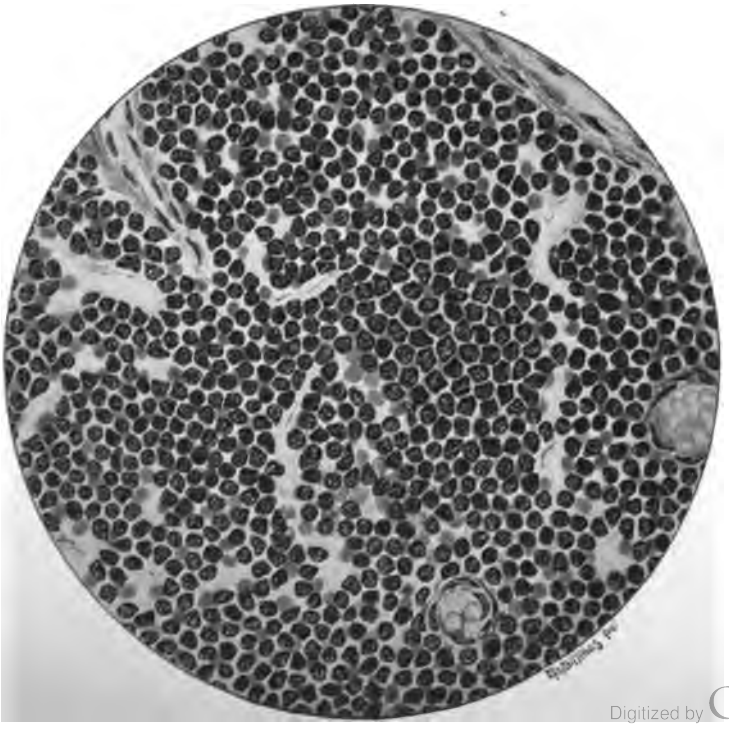
PLATE XIII

FIG. 1



Lymphocytoma of Parotid Gland.
From a case showing xerostomia as the chief clinical feature.

FIG. 2



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Lymphocytoma of the Intestine.

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PLATE XIV

Lymphocytoma of the Ileum and Mesenteric Glands.

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the lymphoid growths, enormous tumors may again develop within it during a relatively brief space of time.

Hodgkin's Disease.—Although this subject will be discussed fully elsewhere it is proper here to call attention to the variety of pathological conditions found in cases corresponding clinically to the classical symptom complex of this affection. By many writers the forms of lymphocytoma described above are regarded as Hodgkin's disease or pseudoleukæmia. Other writers (Reed, Longcope, MacCallum, etc.) regard as the essential histological changes of Hodgkin's disease a process very different from that of lymphoma or lymphosarcoma, and which is characterized by changes resembling a chronic inflammatory process, consisting of proliferations of endothelial and reticular cells, formation of giant cells, presence of many eosinophiles, and a progressive fibrosis. The writer agrees that such a distinct pathological condition exists. He has found it in about a third of his pathological cases diagnosed clinically as Hodgkin's disease. Of the other cases, the majority showed a histological picture of lymphocytoma, two cases presented the picture of a diffuse epithelioid tuberculosis without caseation, one case showed myeloid changes in the nodes, and another the picture of a hæmangio-sarcoma. The clinical complex of Hodgkin's disease as given at the present time has, therefore, no pathological entity, but may be produced by a variety of conditions quite different in nature. The differential diagnosis of these is easily accomplished by the microscopic examination of an excised node. At the present time it would appear wisest to limit the pathological diagnosis of Hodgkin's disease to the chronic inflammatory type of Reed, Longcope, etc., until its etiological nature is discovered. It is convenient to speak of it as the *endothelioid* type of Hodgkin's disease. (See Hodgkin's Disease.)

Leukæmia.—In lymphatic leukæmia the lymph nodes may be primarily involved. Single nodes, single groups, or all of the lymph glands of the body may become enormously enlarged, as the result of an active hyperplasia of the lymphoid elements. The microscopic picture cannot, aside from the great numbers of white cells in the blood, be distinguished from that of lymphocytoma. The same nodular or diffuse formation of atypical lymphoid tissue takes place in the liver, lungs, kidneys, spleen, bone-marrow, etc. The clinical features of leukæmic lymphocytoma are usually those of a more malignant condition than the aleukæmic form. The spleen is usually greatly enlarged, there is often a marked tendency to hemorrhage, there is greater prostration, and the cases usually run a more rapid course. A fatal termination may be reached within limits varying from a few months to two or three years. Under careful treatment with arsenic and Röntgen irradiation the fatal event may be postponed, in some cases for a year or two. (See Leukæmia.)

It is a question as to whether myeloid changes occur primarily in the lymph nodes. A few cases suggesting this have been observed, and the writer has reported a remarkable case originally showing the clinical and pathological features of an endothelioid Hodgkin's. Two years after the operative removal of the enlarged cervical nodes, recurrence took place and while under treatment with Röntgen irradiation a lymphatic leukæmia gradually developed. The study of the nodes, spleen, bone marrow, liver infiltrations, nodules, etc., showed throughout the picture of a myeloid change ("myeloid sarcoma"). It is impossible at the present time properly to classify such a condition.

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Lymphatic Constitution.—The condition of lymphatic constitution or lymphatism (status lymphaticus) is discussed under diseases of the thymus. In the early stages of this affection there may be found in the thymus, lymph nodes, spleen, and bone-marrow a condition of lymphoid hyperplasia somewhat like that of aleukæmic lymphocytoma. In the later stages the lymph nodes and spleen may be atrophic, and the proliferations of endothelium and reticulum may give a picture suggesting that of the endothelioid type of Hodgkin's disease. Indeed, it cannot be said at the present time that such cases are not on the borderland between conditions of chronic inflammatory hyperplasia and Hodgkin's disease or lymphocytoma. In the case of the so-called lymphatic constitution it is very probable that no definite pathological and etiological entity exists, but that it represents the various stages of reaction to a chronic lymphoid or myeloid intoxication having a varied etiology and pathology. The hyperplasia of the thymus becomes the feature of chief interest, and this may be regarded as an essential feature of the lymphoid hyperplasia or as of the nature of a compensatory hypertrophy. (See Hypertrophy of the Thymus.)

Primary Neoplasms.—Aside from the various forms of lymphocytoma, primary tumors of the lymph nodes are rare. They differ from the former in that they arise in single nodes, quickly break through the capsule, and invade the surrounding tissues. The neighboring lymph nodes are affected only through direct involvement. Metastasis is hæmatogenous and not through the lymphatics. Round-cell and spindle-cell fibrosarcoma, angiosarcoma, and endothelioma have been observed. The alveolar endotheliomata are often mistaken for carcinoma, and have been regarded by some writers as primary lymph-node carcinomata. The writer has seen a case of generalized angiosarcoma of the lymph nodes resembling in all respects clinically Hodgkin's disease.

Cysts of the lymph nodes arise through the dilatation of the lymph sinuses with secondary atrophy of the lymphoid tissue. Many of the mesenteric cysts arise in this way, and the writer has seen cases in which the mesentery was studded with cysts, each one arising in a lymph node.

In the cervical region branchial cysts are often found completely surrounded by lymphoid tissue. Not infrequently such nodes are removed under the impression that they are tuberculous.

HÆMOLYMPH NODES.

The general pathology of the hæmolymph nodes is essentially the same as that of the lymphatic glands. Inflammation, syphilis, tuberculosis, the various retrograde changes, and secondary neoplasms may all be found in the nodes containing blood sinuses. Of their special pathology but little is known.

Pernicious Anæmia.—In the majority of cases of this disease the hæmolymph nodes of the prevertebral region are hyperplastic, very red or brown in color, and often increased in number. On microscopic examination the chief feature is the great increase in the number of red cell destroying phagocytes in the blood sinuses, and the large amount of blood pigment present. The number of phagocytes containing blood pigment may exceed that in the spleen, liver, or bone-marrow. Great numbers of mononuclear eosino-

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philes may be present. In certain forms of pernicious anæmia the hæmolymph nodes must be regarded as a seat of excessive hæmolytic action.

Posthemorrhagic Anæmia.—In a fatal case of epistaxis due to a hæmangiomatous polyp the prevertebral hæmolymph nodes showed myeloid changes.

Banti's Disease.—In four cases of splenic anæmia with early and late stages of hepatic cirrhosis the prevertebral hæmolymph nodes showed marked hyperplasia and excessive destruction of red cells. A distinct new formation of hæmolymph nodes was seen in the prevertebral and mesenteric fat tissue.

Leukæmia.—In many cases of leukæmia the prevertebral hæmolymph nodes show more marked changes than do the ordinary lymphatic nodes. Lymphoid and myeloid metaplasias and hyperplasias occur, and the earlier involvement of the hæmolymph nodes points to some special relationship in function to that of the bone-marrow.

Pseudomelanosis.—Pseudomelanosis of the hæmolymph nodes has been observed by the writer in a number of cases of generalized infection with the colon bacillus. Only the hæmolymph nodes presented the change, the deep black color being due to a union of the hydrogen sulphide contained in the blood and tissues with the hæmosiderin of these nodes.

Reaction to Infection.—In all infections characterized by a general intoxication the hæmolymph nodes show a marked reaction. This is particularly the case in streptococcus infections. Marked proliferation of the endothelium of the blood sinuses occurs, and there is greatly increased phagocytosis. Numerous mast cells, mononuclear eosinophiles, and giant cells may appear in the nodes in subacute or chronic infections. The amount of hæmosiderin contained in the nodes may be so great as to give them a deep chocolate-brown color. The neighboring lymphatic nodes in such cases may be devoid, or nearly so, of pigment.

These findings go far to show that the hæmolymph nodes have a function distinct from that of the ordinary lymph nodes, and that it is in some special way concerned with blood destruction and hæmatopoiesis, and also most probably with the processes of protection and immunity. The determination of the exact nature of this function must be left to the future.

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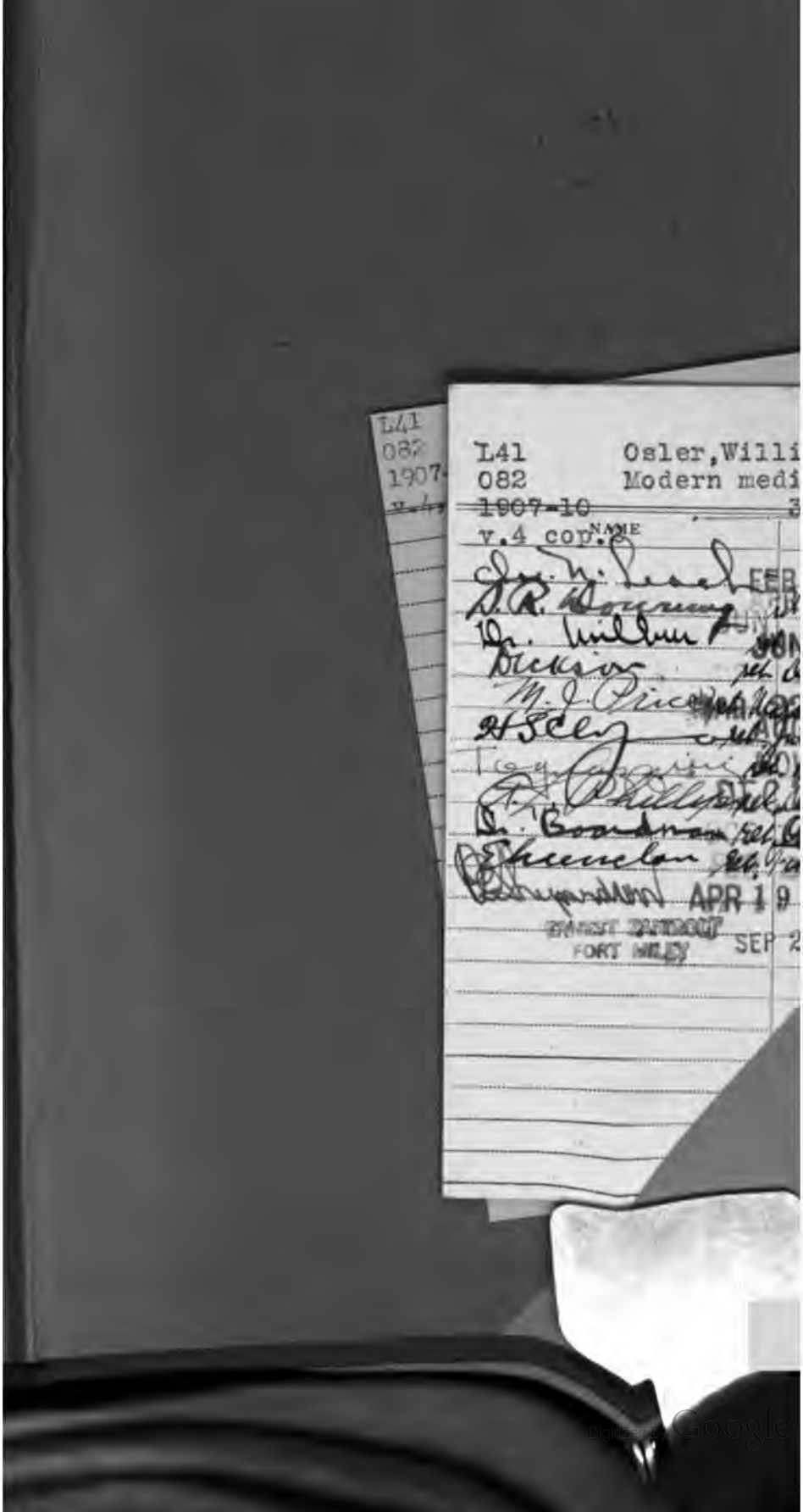
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